SUBSTITUENT EFFECTS FOR SOME SUBSTITUTED 3-BENZYL-2-PHENYL-1,3-THIAZOLIDIN-4-ONES USING ^{1}H AND ^{13}C NMR

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Abstract

Substituents placed on the phenyl rings of 3-benzyl-2-phenyl-1,3-thiazolidin-4-one affect the electron density surrounding both the methine proton, H_m, at C(2), H_a and H_b at C(5), and H_c and H_d at the benzyl carbon. The electron density changes are also exhibited at the C(2), C(4), C(5) and the benzyl carbons. These electron density changes are reflected, respectively, in the differing chemical shifts for the ^{1}H and ^{13}C NMR spectra for these atoms relative to the unsubstituted compound. Correlations for the effects of various substituents in both the 2-phenyl and 3-benzyl rings with the ^{1}H and ^{13}C chemical shifts, for the aforementioned sites, are discussed using Hammett σ constants. The large chemical shift difference observed for the geminal N-benzylic protons, H_c and H_d is discussed.

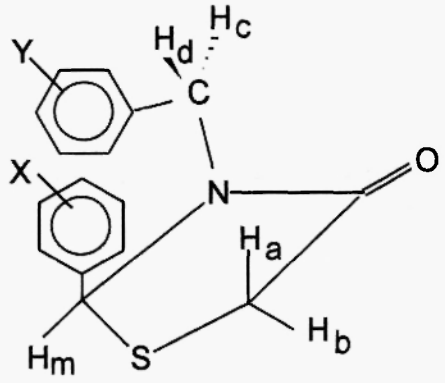
Introduction

Previously, we have described[1] the substituent effects on C(2), C(4) and C(5) sites in the heterocyclic ring, from the phenyl rings, using ^{13}C data for two series of substituted 2,3-diphenyl-1,3-thiazolidin-4-ones. Also, for the same series of compounds the effects of the substituents on the methine proton and the protons at C(5) utilizing ^{1}H NMR have been shown. These compounds and their 1:1 triphenyltin chloride complexes are of interest because of their previously described biological activity.[2] A QSAR study[3] for the activity of these tin complexes against *Ceratocystis ulmi*, shows increased efficacy over other tin adducts.

Obtaining a better understanding of the electronic effects in the thiazolidinones before they are used as ligands will help in the design of more effective complexes in the future. Hence, the reason for our present study[4].

Two series of *para*-substituted 3-benzyl-2-phenyl-1,3-thiazolidin-4-ones were prepared with the substituents placed in either the phenyl ring (Series 1) or the benzyl ring (Series 2). We report the high

resolution ^1H NMR chemical shift results (Table 1) for Series **1** and **2**; the methine proton (H_m), methylene protons at C(5), H_a and H_b, and benzylic protons, H_c and H_d, are shown in structure **1**. The ^{13}C chemical shift data for sites C(2), C(4) and C(5) in the heterocyclic ring, in addition to the N-benzyl carbon, are reported in Table 2.



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Series 1		Series 2	
X	Y	X	Y
4-F	H	H	4-Cl
4-Cl	H	H	4-Me
4-F	H	H	4-MeO
4-Br	H		
4-I	H		
H	H		
4-Me	H		
4-MeO	H		

In our previous study[1] of two different series of substituted 2,3-diphenylthiazolidinones, we looked at the electronic effects at the same sites as those described here for the title compounds. However, in this series there is an additional N-benzyl carbon with two protons (H_c and H_d). Of further interest is the fact that the N-benzyl carbon is sp^3 hybridized, and this could affect the transmission of electronic effects into the thiazolidinone ring. Transmission of substituent effects has been previously shown[1] to be very effective from the N-phenyl ring in the substituted 2,3-diphenylthiazolidinone series. Hammett correlations using σ values[5] for series **1** and **2** are discussed for these new substituted thiazolidinones. Because steric effects were noted for *meta*-substituted compounds in previous work,[1] which obviously affects the usefulness of Hammett correlations, only *para*-substituted molecules have been considered in this study. Also, the range of substituents is more limited in this study than the previous work.[1]

Results and Discussion.

Listed in Table 1 are the methine (H_m) and N-benzyl ^1H chemical shifts for both the Series **1** and **2** compounds, with substituents in the 2-phenyl and 3-benzyl rings, respectively. In concert with observations for the substituted diphenylthiazolidinones, no Hammett correlations (Equation 1) were observed for Series **1** compounds. A correlation was previously observed from the N(3)-phenyl ring.[1] The benzyl carbon, in this series, appears to block any measurable transmission effects from the N(3)-benzyl ring to the methine proton (H_m).

$$\delta - \delta_o = \rho\sigma \qquad (1)$$

Table 1. ^{1}H NMR chemical shifts (ppm) for substituted 3-benzyl-2-phenyl-1,3-thiazolidinones

Compound	Substituent X	Substituent Y	H_m	H_c (J, Hz)	H_d (J, Hz)
1a	*p*-F	H	5.35	5.13, 5.08 (14.7)	3.53, 3.48 (14.7)
1b	*p*-Cl	H	5.32	5.14, 5.09 (14.7)	3.52, 3.47 (14.7)
1c	*p*-Br	H	5.30	5.14, 5.09 (14.7)	3.52, 3.47 (14.7)
1d	*p*-I	H	5.28	5.15, 5.09 (14.8)	3.52, 3.45 (14.8)
1e	H	H	5.36	5.16, 5.11 (14.7)	3.53, 3.48 (14.7)
1f	*p*-Me	H	5.33	5.15, 5.10 (14.7)	3.52, 3.47 (14.7)
1g	*p*-OMe	H	5.34	5.12, 5.07 (14.7)	3.52, 3.47 (14.7)
2a	H	*p*-Cl	5.35	5.06, 5.01 (14.8)	3.56, 3.52 (14.8)
2b	H	*p*-Me	5.38	5.16, 5.12 (14.6)	3.51, 3.46 (14.6)
2c	H	*p*-OMe	5.37	5.11, 5.06 (14.4)	3.49, 3.44 (14.4)

The N-benzyl protons (H_c and H_d) are clearly diastereotopic,[6,7] exhibiting two doublets. However, unlike the C(5) methylene protons (H_a and H_b) which show the same signal characteristics with a chemical shift difference of 0.2 ppm, the N-benzyl protons have chemical shift differences of approximately 1.5 ppm (Table 1). Staskum[8] noted large chemical shift differences for nonequivalent geminal methylene protons for hindered N-substituted acetanilides and difluorooxyboranes. Staskum's compounds had chemical shift differences from 0.6 to 1.2 ppm for the methylene signals. There is no detectable interaction for Series **1** substituents and the N(3)-benzyl protons, (H_c and H_d). There is a Hammett correlation for Series **2** substituents with H_d at the N(3)-benzyl site [equation, $\delta - \delta_o = 6.92\sigma - 0.008$, ($r = 0.99$; $n = 4$)]. The large, positive ρ value indicates a preference for a significant negative charge build-up at proton H_d. The large shift difference for protons H_c and H_d in **1e** had previously been reported by Woolston, *et al*;[6] the significant downfield shift for proton H_c points to a strong hydrogen bonding interaction and also accounts for the hindered rotation of the N-benzyl carbon.

The ^{13}C data for the heterocyclic ring and the N-benzyl carbon for Series **1** and **2** are listed in Table 2. Using the substituent chemical shift values derived from the data for the *para*-substituted compounds for sites C(2), C(4) and C(5), in Series **1**, no sensitivity to substituents was observed using Hammett σ values[5] (Table 3). This was contrary to our observations of substituent behavior from substituents at the C(2) phenyl ring in the diphenylthiazolidin-4-one series and could be due in this case to smaller range of electron withdrawing and donating ability of the substituents. In this new series there is an additional ^{13}C site, C(6), at the N-benzyl carbon; C(6), Series **1**, did show a Hammett correlation (equation, $\delta - \delta_o = 0.47\sigma - 0.019$; $r = 0.98$; $n = 7$). The positive ρ value indicates a preference for negative charge build-up at the N-benzyl carbon for substituents on the C(2) phenyl ring.

Table 2. ^{13}C NMR chemical shifts (ppm) for substituted 3-benzyl-2-phenyl-1,3-thiazolidin-4-ones

compound	substituent X	substituent Y	C(2)	C(4)	C(5)	N-C
1a	*p*-F	H	62.01	170.99	32.93	46.16
1b	*p*-Cl	H	62.06	171.08	32.96	46.27
1c	*p*-Br	H	62.06	171.01	32.91	46.22
1d	*p*-I	H	62.16	171.05	32.92	46.23
1e	H	H	62.67	171.15	32.97	46.16
1f	*p*-Me	H	62.51	171.08	32.99	46.06
1g	*p*-OMe	H	62.44	171.00	33.06	46.01
2a	H	*p*-Cl	62.71	171.21	32.89	45.54
2b	H	*p*-Me	62.59	171.17	33.04	45.88
2c	H	*p*-OMe	62.60	171.09	33.08	45.55

Series **2** compounds exhibited Hammett correlations, using ^{13}C chemical shifts, for C(2), C(4), and C(5), and the results are shown in Table 3. The ρ values of 0.26 [C(2)], 0.24 [C(4)] and –0.39 [C(5)] indicate that C(2) and C(4) prefer a negative charge build-up and C(5) prefers a positive charge build-up. The previous study[1] of the substituted diphenylthiazolidin-4-ones only showed a Hammett correlation for

Table 3. Results of Hammett correlations using ^{13}C NMR data for *para*-substituted compounds, Series **1** and **2.**

SERIES	Site	ρ	constant	r	n
1	C(6)	0.47	-0.019	0.98	8
2	C(2)	0.26	-0.009	0.98	4
2	C(4)	0.24	0.003	0.97	4
2	C(5)	-0.39	-0.003	0.99	4

C(2) where the preferred charge build-up was positive. The presence of the N-benzyl, sp^3-hybridized carbon does not appear to unduly interfere with the transmission of electronic effects into the heterocyclic ring. However, there was no apparent Hammett correlation for the N(3)-benzyl carbon from substituents in that phenyl ring.

Experimental

The thiazolidine-4-ones were prepared using the procedure previously described.[9] Melting points are

uncorrected; a Mel-Temp apparatus was used. All spectra were recorded on a GE QE-300 at 298 K observing ^{1}H and ^{13}C at 300.15 and 75.48 MHz, respectively. All samples were dissolved in $CDCl_3$ at a concentration of 100 mg/mL using precision bore 5 mm nmr tubes supplied by Norell, Inc.

^{1}H spectra were collected as sets of 32K data points over a spectral width of 3.012 kHz using a 30° pulse; pulse width, 3.0 μs; acquisition time, 2.72 s; relaxation delay, 1.0 s; number of scans, 16. ^{13}C spectra were collected into 16K data sets over a spectral width of 20 kHz using a 60° observe pulse using Waltz-16 decoupling; pulse width, 6.0 μs; acquisition time 409.60 ms; relaxation delay, 2.00 s; number of scans 1492. The spectrometer was locked to the deuterium resonance of the solvent ($CDCl_3$), and all chemical shifts were referenced to internal TMS (δ = 0.00 ppm). ^{1}H coupling constants are shown in the relevant tables. Each spectrum was only acquired once. Previous experiments have shown that the chemical shift values for both ^{1}H and ^{13}C spectra vary by less than 0.1% when acquiring the same spectrum multiple times on the same spectrometer.[1] Further, this error is the same when comparing the same spectrum acquired on a GE Q-300 versus a Bruker WP80.[7,11] Elemental analyses on all samples were performed by Galbraith Laboratories, Inc., 2323 Sycamore Drive, Knoxville, TN 37921-1750 USA. 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 yields. Hammett correlations were obtained using Excel.[12]

3-benzyl-2-(4-fluorophenylthiazolidin-4-one (**1a**) (37%); m.p. 107-108 °C, Anal. Found: C, 67.02; H, 5.01; N, 4.80. Calc. For $C_{16}H_{14}NOSF$: C, 66.88; H, 4.91; N, 4.87; ^{1}H NMR, 6.85-7.41 (9H, m, aromatics), 5.35 (1H, s, CH), 3.71-3.89 (2H, doublets, CH_2), 5.08-5.13 and 3.48-3.53 (2H, doublets, CH_2). ^{13}C NMR, 170.99 (C-4), 135.12, 134.79, 129.12-127.92, 116.17,115,88 (12, Ar-C), 62.01 (C-2), 46.16 (N-C), 32.93 (C-5).

3-benzyl-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (**1b**) (12%); m.p. 86-87 °C, Anal. Found: C, 63.96; H, 4.89; N, 4.54. Calc. for $C_{16}H_{14}NOSCl$: C, 63.26; H, 4.64; N, 4.61; ^{1}H NMR, 7.15-7.31 (9H, m, aromatics), 5.32 (1H, s, CH), 3.71-3.88 (2H, doublets, CH_2), 5.09-5.14 and 3.47-3.52 (2H, doublets, CH_2). ^{13}C NMR, 171.08 (C-4), 137.69, 135.07, 129.32-128.02 (12, Ar-C), 62.06 (C-2), 46.27 (N-C), 32.96 (C-5).

3-benzyl-2-(4-bromophenyl)-1,3-thiazolidin-4-one (**1c**) (33%); m.p. 67-68 °C; Anal. Found: C, 55.22; H, 4.07; N, 4.04. Calc. for $C_{16}H_{14}NOSBr$: C, 55.18; H, 4.05; N, 4.02; ^{1}H NMR, 7.15-7.46 (9H, m, aromatics), 5.30 (1H, s, CH), 3.70-3.88 (2H, doublets, CH_2), 5.09-5.14 and 3.47-3.52 (2H, doublets, CH_2). ^{13}C NMR, 171.01 (C-4), 138.20, 135.03, 132.22, 128.86-127.98, 123.10 (12, Ar-C), 62.06 (C-2), 46.22 (N-C), 32.91 (C-5).

3-benzyl-2-(4-iodophenyl)-1,3-thiazolidin-4-one (**1d**) (90%); m.p. 114-115 °C; Anal. Found: C, 48.81; H, 3.63; N, 3.57. Calc. for $C_{16}H_{14}NOSI$: C, 48.62; H, 3.57; N, 3.54; ^{1}H NMR, 6.97-7.65 (9H, m, aromatics), 5.28 (1H, s, CH), 3.69-3.88 (2H, doublets, CH_2), 5.09-5.15 and 3.45-3.52 (2H, doublets, CH_2).

^{13}C NMR, 171.05 (C-4), 138.88, 138.19, 134.99, 128.97-127.96 (12, Ar-C), 62.16 (C-2), 46.23 (N-C), 32.92 (C-5).

3-benzyl-2-phenyl-1,3-thiazolidin-4-one (**1e**) (75%); uncorrected m.p. 151-152 °C (lit. m.p.153-154).[13]

3-benzyl-2-(4-methylphenyl)-1,3-thiazolidin-4-one (**1f**) (37%); m.p. 60-61 °C; Anal. Found: C, 72.06; H, 6.17; N, 4.85. Calc. for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94; ^{1}H NMR, 7.05-7.38 (9H, m, aromatics), 5.33 (1H, s, CH), 3.69-3.89 (2H, doublets, CH_2), 5.10-5.15 and 3.47-3.52 (2H, doublets, CH_2), 2.35 (3H, s, Ar-CH_3). ^{13}C NMR, 171.08 (C-4), 139.08, 136.06, 135.39, 129.73-127.12 (12, Ar-C), 62.51 (C-2), 45.06 (N-C), 32.99 (C-5), 21.25 (Ar-CH_3).

3-benzyl-2-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**1g**) (19%); m.p. 58-59 °C; Anal. Found: C, 68.52; H, 5.80; N, 4.68. Calc. for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68; ^{1}H NMR, 6.82-7.39 (9H, m, aromatics), 5.34 (1H, s, CH), 3.70-3.89 (2H, doublets, CH_2), 5.07-5.12 and 3.47-3.52 (2H, doublets, CH_2), 3.79 (3H, s, $ArOCH_3$). ^{13}C NMR, 171.00 (C-4), 135.37, 130.65, 128.67-127.81, 114.35 (12, Ar-C), 62.44 (C-2), 55.32 Ar-OCH_3), 46.01 (N-C), 33.06 (C-5).

3-(4-chlorobenzyl)-2-phenyl-1,3-thiazolidin-4-one (**2a**) (20%); m.p. 159-160 °C; Anal. Found: C, 63.65; H, 4.81; N, 4.54, Calc. for $C_{16}H_{14}NOSCl$: C, 63.25; H, 4.64; N, 4.61; ^{1}H NMR, 7.06-7.43 (9H, m, aromatics), 5.35 (1H, s, CH), 3.77 - 3.97 (2H, doublets, CH_2), 5.01-5.06 and 3.52-3.56 (2H, doublets, CH_2). ^{13}C NMR, 171.17 (C-4), 138.77, 133.79, 129.76-127.13 (12, Ar-C), 62.71 (C-2), 45.88 (N-C), 33.04 (C-5).

3-(4-methylbenzyl)-2-phenyl-1,3-thiazolidin-4-one (**2b**) (28%); m.p. 134-135 °C; Anal. Found: C, 72.42; H, 6.23; N, 4.83, Calc. for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94; ^{1}H NMR, 6.98-7.38 (9H, m, aromatics), 5.38 (1H, s, CH), 3.70 - 3.91 (2H, doublets, CH_2), 5.12-5.16 and 3.46-3.51 (2H, doublets, CH_2), 2.33 (3H, s, $ArCH_3$). ^{13}C NMR, 171.12 (C-4), 139.19, 137.62, 132.16, 129.38-127.09 (12, Ar-C), 62.59 (C-2), 45.88 (N-C), 33.04 (C-5), 21.06 (Ar-CH_3).

3-(4-methoxybenzyl)-2-phenyl-1,3-thiazolidin-4-one (**2c**) (10%); m.p. 147-148 °C; Anal. Found: C, 68.48; H, 5.83; N, 4.55, Calc. for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68; ^{1}H NMR, 6.79-7.38 (9H, m, aromatics), 5.37 (1H, s, CH), 3.69 - 3.89 (2H, doublets, CH_2), 5.06-5.11 and 3.44-3.49 (2H, doublets, CH_2), 3.77 (3H, s, $ArOCH_3$). ^{13}C NMR, 171.09 (C-4), 159.22, 139.18, 129.77-127.10, 114.03 (12, Ar-C), 62.60 (C-2), 55.21 Ar-OCH_3), 45.57 (N-C), 33.08 (C-5).

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REFERENCES

(1) J. Tierney, G. Houghton, K. Sanford, L. Mascavage, M. McCoy, A. Findeisen and J. Kilburn, *Magn. Reson. Chem.*, **34**, 573, (1996).
(2) G. Eng, D. Whalen, Y. Z. Zhang, J. Tierney, X. Jiang and L. May, *Appl. Organomet., Chem.*, **10**, 495, (1996).
(3) G. Eng, D. Whalen, P.Musingarimi, J. Tierney and M. DeRosa, *Appl. Organomet. Chem.*, **12**, 25, (1998).
(4) Paper [ORGN 567] presented at the 206th National Meeting of the American Chemical Society; Boston, Massachusetts; August 24-28, 1998.
(5) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.*, **91**, 165, (1991).
(6) C. R. J. Woolston, J. B. Lee, F. J. Swinbourne and W. A. Thomas, *Magn. Reson. Chem.*, **30**, 1075, (1992).
(7) C. R. J. Woolston, J. B. Lee and F. J. Swinbourne, *Mag. Res. Chem.*, **31**, 348, (1993).
(8) B. Staskum, *J. Org. Chem.* **46**, 1643 (1981)
(9) J. Tierney, *J. Heterocyclic Chem.* **26**, 997, (1989).
(10) A. R. Surrey, *J. Am. Chem. Soc.*, **69**, 2911, (1947).
(11) C. R. J. Woolston, J. B. Lee and F. J. Swinbourne, *Mag. Res. Chem.*, **30**, 1075, (1992).
(12) Excel 97 is a registered trademark of Microsoft Corporation.
(13) H. D. Troutman and L. M. Long, *J. Am. Chem. Soc.*, **70**, 3436, (1948).

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