A SECOND STUDY - PREDICTING THE ^{13}C CHEMICAL SHIFTS FOR A SERIES OF SUBSTITUTED 3-(4-METHOXYPHENYL)-2-PHENYL-1,3-THIAZOLIDIN-4-ONES

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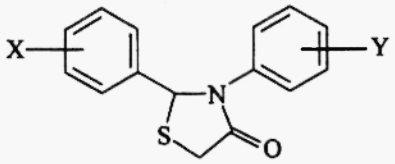
Abstract: Previously, an 'additivity' equation relating experimental ^{13}C chemical shift data for two *mono*-substituted diphenyl-1,3-thiazolidin-4-one series was developed to predict chemical shifts for a similarly substituted *bis*-disubstituted thiazolidinone series. The sites of interest in the 1,3-thiazolidin-4-one are the C-2, C-4, and C-5 carbons. The empirically derived equation for predicting the chemical shifts is $\delta_{XY} = \delta_H + (\delta_X - \delta_H) + (\delta_Y - \delta_H)$ 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 substituted-2-phenyl-3-methoxyphenyl-1,3-thiazolidin-4-ones, where the substituents on both phenyl rings are not the same. The equation was shown to predict a less exact chemical shift in this one test series than for the previous *bis*-disubstituted series of compounds.

Introduction

The genesis for our interest in the synthetic routes to 1,3-thiazolidin-4-ones, and the spectroscopic properties of the products formed have been indicated extensively before.[1-6] In our previous study, we reported the relationship between the experimental chemical shift values for two series of monosubstituted 2,3-diphenyl-1,3-thiazolidin-4-ones and a related *bis*-(disubstituted)- 2,3-diphenyl-1,3-thiazolidin-4-one series.[1] A reasonably good correlation was obtained between experimental and predicted values for the ^{13}C chemical shifts when applying Equation 1. The series of compounds used to develop the relationship of Equation 1 is shown in Figure 1.



Series 1: X = *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *p*-Br, *m*-Br, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *m*-OCH_3; Y = H

Series 2: Y = *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *p*-Br, *m*-Br, H, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *m*-OCH_3; X = H

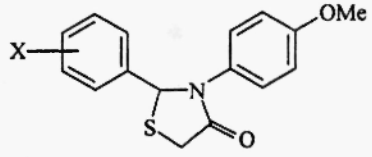
Series 3: X = Y = *p*-NO_2, *m*-NO_2, *p*-F, *m*-F, *p*-Cl, *p*-Br, *m*-Br, *p*-CH_3, *m*-CH_3, *p*-OCH_3, *m*-OCH_3

Figure 1

$$\delta_{XY} = \delta_H + (\delta_X - \delta_H) + (\delta_Y - \delta_H) \qquad \textbf{Equation 1}$$

In Equation 1 δ_H is the chemical shift for the unsubstituted compound, δ_X is the chemical shift observed for Series 1 compounds, δ_Y is the chemical shift observed for Series 2 compounds, and δ_{XY} is the predicted chemical shift for the compounds in Series 3.

The target molecules of interest for this study are shown in Figure 2. Previously,[1-4] we have also utilized the experimental data for the ^{13}C chemical shifts to show the 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 continuation study is discussed here.



Series 4: X = (a) *p*-NO_2, (b) *m*-NO_2, (c) *p*-F, (d) *m*-F, (e) *p*-Cl, (f) *m*-Cl, (g) *p*-Br, (h) *m*-Br, (i) H, (j) *p*-Me, (k) *m*-Me, (l) *p*-MeO, (m) *m*-MeO,

Figure 2

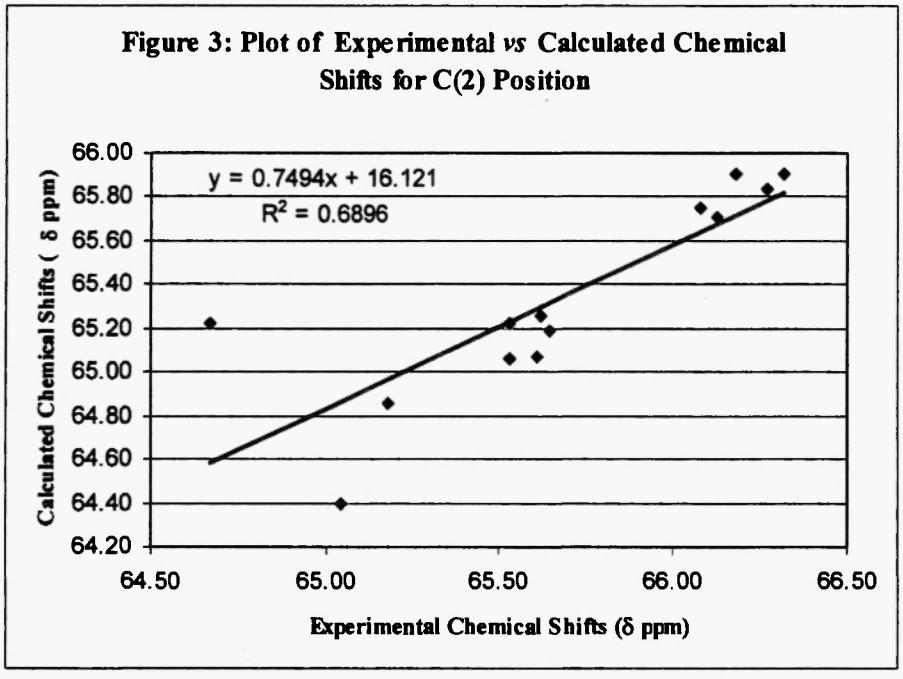
Results and Discussion.

The predicted and experimental ^{13}C chemical shifts for the C(2), C(4) and C(5) sites for Series 4, the compounds under investigation, are shown in Table 1. The one immediately obvious result is that unlike the *bis*-disubstituted compounds that showed relatively good predictability with less than $\pm$ 0.1 ppm in most cases ,[1] that is not the case in this instance. The average deviation for predicted versus the experimental chemical shifts are all positive: C(2) + 0.34 ppm ; C(4) + 0.32 ppm; C(5) + 0.25 ppm.

Table 1: Experimental and Calculated (in parenthesis) ^{13}C Chemical Shift Data for Substituted-2-phenyl-3-(4-methoxypheny)-thiazolidin-4-ones in ppm relative to TMS.

compound	Substituent X	C(2)	C(4)	C(5)
4a	*p*-NO_2	65.04 (64.40)	171.09 (170.78)	33.55 (33.16)
4b	*m*-NO_2	65.18 (64.86)	171.10 (170.91)	33.61 (33.34)
4c	*p*-F	65.62 (65.26)	171.29 (171.00)	33.57 (33.38)
4d	*m*-F	64.67 (65.22)	171.26 (171.06)	33.69 (33.24)
4e	*p*-Cl	65.61 (65.07)	171.27 (170.83)	33.66 (33.27)
4f	*m*-Cl	65.53 (65.22)	171.29 (170.98)	33.57 (33.26)
4g	*p*-Br	65.65 (65.19)	171.27 (170.87)	33.64 (33.30)
4h	*m*-Br	65.53 (65.06)	171.29 (171.10)	33.56 (33.36)
4i	H	66.32 (65.91)	171.45 (171.10)	33.69 (33.36)
4j	*p*-CH_3	66.18 (65.91)	171.47 (171.10)	33.74 (33.38)
4k	*m*-CH_3	66.27 (65.84)	171.55 (171.10)	33.69 (33.34)
4l	*p*-OCH_3	66.08 (65.75)	171.38 (171.11)	33.79 (33.49)
4m	*m*-OCH_3	66.13 (65.71)	171.49 (171.13)	33.67 (34.30)

A plot of the experimental versus the calculated chemical shifts for C(2) is shown in Figure 3. One value for the *m*-fluoro substituted compound **4d** shows a significant deviation from the trendline. The calculated chemical shift for the *bis-meta*-difluoro compound, Series 3, has previously been noted to have had the largest deviation between reported and calculated values .[1] Clearly, the *meta*-fluoro substituent is problematic in these studies for reasons yet to be discerned. The C(2) position under investigation is in direct line of transmission for substituent effects from the C(2) phenyl ring, and it is interesting that the *p*-nitro and *p*-methoxy substituents are not causing marked deviations. If the *meta*-fluoro value is removed from the analysis at C(2), a much improved correlation between predicted and experimental values with a trendline equation $y = 1.11x - 7.96$ ($R^2 = 0.964$) is obtained. Electronic effects at C(2) from substituent changes at the C(2)-phenyl ring are the most marked of all. No clear direct relationship appears to exist when comparing predicted and experimental chemical shift values at C(4) and C(5). These sites are more remote from the C(2)-phenyl ring and may be masked by the close proximity of the *p*-methoxy group on the N(3)-phenyl ring.



In previous studies[1-4] we have also looked for transmission of effects by relating substituent chemical shift values (SCS) to both Hammett (Equation 2) and Swain-Lupton (Equation 3) approaches. Previous studies have shown that there is a greater sensitivity with the Swain-Lupton approach over the Hammett constants when determining substituent effects in this complex thiazolidinone system. Interestingly, even though the direct prediction for the chemical shift values using Equation 1 can be made, the experimental values did show resilience

$$\delta - \delta_o = \rho\sigma \qquad \textbf{Equation 2}$$

$$\delta - \delta_o = fF + rR \qquad \textbf{Equation 3}$$

when applying the usual, classic substituent chemical shift (SCS) approach. The Hammett equation proved to be marginally less effective in determining substituent chemical shift effects than with previous studies. This is probably due to the presence of the powerful *p*-methoxy group on the (N)-3-phenyl ring. Again, there was an improvement in correlations where only the *para*-substituted values were used. This was most marked when utilizing the Swain-Lupton approach; the results are shown in Table 2. The transmission of electronic effects from C(2)-phenyl shows in a more marked manner when applying the Swain Lupton approach, where a greater degree of flexibility is allowed for the transmission of effects from substituent to site. The results from the Swain Lupton correlations show that there is a 13% resonance contribution at C(2), a 15% resonance contribution at C(4), and a 56 % resonance contribution at C(5) when evaluating solely the *para*-substituted compounds.

Table 2. Swain-Lupton Dual Substituent Parameter Correlations for ^{13}C Substituent Chemical Shifts for Series 4.

site	Equation	Correlation Coefficient	Comments
C(2)	SCS = - 1.62F - 0.77R - 0.17	$R^2 = 0.796$	*meta* and *para* substituents (minus *m*-F value)
	SCS = - 1.60F - 0.47R + 0.08	$R^2 = 0.952$	*para* substituents
C(4)	SCS = - 2.94F - 1.37R - 0.03	$R^2 = 0.539$	*meta* and *para* substituents
	SCS = - 0.51F - 0.09R + 0.02	$R^2 = 0.949$	*para* substituents only
C(5)	SCS = 0.02F - 0.40R - 0.28	$R^2 = 0.130$	*meta* and *para* substituents
	SCS = - 0.20F - 0.25R	$R^2 = 0.980$	*para* substituents only

Conclusion

Equation 1, which was previously formulated from the linear combination of two monosubstituted series of thiazolidinone chemical shift values, does not appear to be as accurate at predicting the chemical shifts of dissimilarly disubstituted thiazolidinones as it has been in predicting the chemical shifts for the *bis*-disubstituted compounds; however, the difference between experimental and predicted values are still less than 1 ppm. The values can be improved by the use of a constant for each of the C(2), C(4) and C(5) cases. Equation 1 when modified to $\square_{XY} = \square_H + (\square_X - \square_H) + (\square_Y - \square_H) + c$, where c is the constant, would give more precise values. The constants 'c' for the modified Equation 1, for C(2), C(4) and C(5) are + 0.34, + 0.31 and + 0.22, respectively. One substituent, the *meta*-fluoro group appears to deviate the most from predicted and experimental values. When utilizing the Swain-Lupton approach to determine the electronic effects derived from the substituents, the *para*-substituted series of compounds exhibit the strongest correlations at the C(2)-phenyl ring to the sites C(2), C(4) and C(5) in the thiazolidinone ring. Because of the complexity of the thiazolidi-4-one system, the greater flexibility afforded by the Swain Lupton approach is more effective than the Hammett equation in its sensitivity for detecting the transmission of electronic effects within the system.

Experimental

The thiazolidine-4-ones were prepared using the procedure previously described[2] by adapting a method originally utilized by Surrey.[7] Melting points are uncorrected; a Mel-Temp apparatus was used. All spectra were recorded on a Bruker 400 at 298K observing ^1H 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.

^1H spectra were collected into 32K data sets over a spectral width of 3012.0 Hz using a 30° pulse; pulse width, 3.0 □s; 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 ±10.000 Hz with a 60° observed pulse using Waltz-16 decoupling; pulse

width, 6.0 □s; acquisition time 409.6 ms; relaxation delay, 2.00 s; number of scans, 512. The spectrometer was locked to the deuterium resonance of the solvent ($CDCl_3$) and all chemical shifts were referenced to internal TMS (□ = 0.00 ppm). 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 μm film thickness, He carrier gas, 1.0 mL/min flow, 80 °C for 1 minute isothermal 15 °C/min to 275 °C then 275 °C for 3 minutes isothermal, injector temp 250 °C, 0 min , 1:50 split. 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 and Swain-Lupton correlations were obtained using Excel in Microsoft Office.

3-(4-Methoxyphenyl)-2-(4-nitrophenyl)-1,3-thiazolidin-4-one (**4a**). Yield 38%; m.p. 167-8 °C; IR: 1668 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.18-6.69 (8H, m, aromatics), 5.88 (1H, s, CH), 3.90, 3.78 (2H, m, CH_2), 3.64 (3 H, s, OCH_3); ^{13}C NMR: δ 171.1 (C4), 159.1, 148.5, 147.2, 129.9, 128.4, 127.5, 124.5, 115.1, 65.0 (C2), 55.7, 33.5 (C5); MS (m/z): 330 (M^+, 100%), $C_{16}H_{14}O_4N_2S$ (330.36).

3-(4-Methoxyphenyl)-2-(3-nitrophenyl)-1,3-thiazolidin-4-one (**4b**). Yield 56 %; m.p. 125-7 °C; IR: 1672 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 8.11-6.73 (8H, m, aromatics), 6.05 (1H, s, CH), 3.96, 3.80 (2H, m, CH_2), 3.66 (3 H, s, OCH_3);^{13}C NMR: δ 171.1 (C4), 159.1, 155.1, 148.8, 142.4, 134.9, 133.5, 130.5, 128.9, 127.5, 114.9, 65.2 (C2), 55.7, 33.6 (C5); MS (m/z) 330 (M^+, 100%), $C_{16}H_{14}O_4N_2S$ (330.36).

2-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**4c**). Yield 30 %; m.p. 117-9 °C;IR: 1669 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.20-6.73 (8H, m, aromatics), 5.91 (1H, s, CH), 3.92, 3.81 (2H, m, CH_2,), 3.68 (3 H, s, OCH_3); ^{13}C NMR: δ 171.3 (C4), 164.5*, 162.0*, 158.9*, 142. 8*, 142.7*, 130.8*, 130.7*, 130.3*, 127.7*, 123.2*, 123.2*, 116.5*, 116.3*, 114.9*, 114.6*, 114.4*, 65.6 (C2), 55.7, 33.6 (C5) [some of the aromatic peaks marked with * are possibly due to carbon-fluorine coupling – no attempt was made to resolve the coupling]; MS (m/z): 303 (M^+, 100%), $C_{16}H_{14}O_2NSF$ (303.36).

2-(3-Fluorophenyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**4d**). Yield 51%; m.p. 123-4 °C; IR: 1667 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.09-6.58 (8H, m, aromatics), 5.78 (1H, s, CH), 3.77, 3.68 (2H, m, CH_2), 3.53 (3 H, s, OCH_3); ^{13}C NMR: δ 171.3 (C4), 164.4, 161.9, 158.9, 135.6, 130.3, 129.6, 129.5, 127.9, 116.3, 114.9, 64.7 (C2), 55.7, 33.7 (C5); MS (m/z): 303 (M^+, 20%), $C_{16}H_{14}O_2NSF$ (303.36).

2-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**4e**) . Yield 56%; m.p. 129-130 °C; IR: 1666 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.07-6.58 (8H, m, aromatics), 5.75 (1H, s, CH), 3.78, 3.67 (2H, m, CH_2), 3.53 (3 H, s, OCH_3); ^{13}C NMR: δ 171.3 (C4), 158.9, 138.5, 135.1, 130.2, 129.4, 129.1, 127.8, 114.9, 65.1 (C2), 55.7, 33.7 (C5). MS (m/z): 319 (M^+, 89%), $C_{16}H_{14}O_2NSCl$ (319.81).

2-(3-Chlorophenyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**4f**). Yield 36%; m.p. 168-9 °C; IR: 1671 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.09-6.59 (8H, m, aromatics), 5.73 (1H, s, CH), 3.78, 3.66 (2H, m, CH_2),
3.53 (3 H, s, OCH_3); ^{13}C NMR: 171.29 (C4), 159.0, 142.5, 132.4, 130.7, 130.5, 130.2, 127.7, 126.1, 123.2, 115.0, 65.5 (C2), 55.7, 33.6 (C5); (m/z) 319 (M^+, 14%), $C_{16}H_{14}O_2NSCl$ (319.81).

2-(4-Bromophenyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**4g**) . Yield 54%; m.p. 138-9 °C; IR: 1663 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.22-6.57 (8H, m, aromatics), 5.74 (1H, s, CH), 3.76, 3.65 (2H, m, CH_2), 3.56 (3 H, s, OCH_3);^{13}C NMR: δ 171.3 (C4), 159.0, 138.5, 135.1, 130.2, 129.4, 129.0, 127. 8, 114.9, 65.6 (C2), 55.7, 33.6 (C5); MS (m/z): 364 (M^+, 70%), $C_{16}H_{14}O_2NSBr$ (364.26).

2-(3-Bromophenyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**4h**). Yield 49%; m.p. 116-18°C; 1671 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.39-6.74 (8H, m, aromatics), 5.87 (1H, s, CH), 3.98, 3.80 (2H, m, CH_2), 3.68 (3 H, s, OCH_3); ^{13}C NMR: δ 171.3 (C4), 159.0, 143.0, 132.4, 130.7, 130.5, 130.2, 127.7, 126.1, 123.2, 115.0, 65.5 (C2), 55.7, 33. 6 (C5). MS (m/z): 364 (M^+, 19%), $C_{16}H_{14}O_2NSBr$ (364.26).

2,3-Diphenylthiazolidin-4-one (**4i**). Yield 60%; m.p. 131-132 °C, (lit.[7] m.p.130-131 °C).

3-(4-Methoxyphenyl)-2-(4-methylphenyl)-1,3-thiazolidin-4-one (**4j**). Yield 12%; m.p. 150-1 °C; IR:1663 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.18-6.69 (8H, m, aromatics), 5.89 (1H, s, CH), 3.91, 3.78 (2H, m, CH_2), 3.65 (3 H, s, OCH_3), 2.22 (3H, CH_3).^{13}C NMR: 171.5 (C4), 158.8, 139.2, 137.0, 130.6, 129.9, 127.8, 127.4, 114.8, 66.2 (C2), 55.7, 33.7 (C5), 21.5; MS (m/z): 299 (M^+, 100%), $C_{17}H_{17}O_2NS$ (299.39).

3-(4-Methoxyphenyl)-2-(3-methylphenyl)-1,3-thiazolidin-4-one (**4k**). Yield 41%; m.p. 92-3 °C; IR: 1663 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.20-6.72 (8H, m, aromatics), 5.89 (1H, s, CH), 3.93, 3.70 (2H, m, CH_2), 3.65 (3 H, s, OCH_3), 2.24 (3H, s, CH_3). ^{13}C NMR: δ 171.5 (C4), 158.7, 140.1, 139.0, 130.6, 130.1, 129.1, 127.9, 127.7, 124.5, 114.8, 66.3 (C2), 55.7, 33.7 (C5), 21.8; MS (m/z): 299 (M^+, 100%), $C_{17}H_{17}O_2NS$ (299.39).

2-(4-Methoxyphenyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**4l**). Yield 54%; m.p. 119-120 °C, (lit.[1] m.p. 119-120 °C).

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-1,3-thiazolidin-4-one (**4m**). Yield51%; m.p. 127-8 °C; IR: 1672 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 7.20-6.72 (8H, m, aromatics), 5.90 (1H, s, CH), 3.91, 3.80 (2H, m, CH_2), 3.79 (3H, s, OCH_3), 3.65 (3 H, s, OCH_3). ^{13}C NMR: δ 171.5 (C4), 160.3, 158.8, 141.7, 130.2, 127.6, 119.5, 114.7, 113.0, 66.1 (C2), 55.7, 55.64, 3.67 (C5); MS (m/z): 315 (M^+, 100%), $C_{17}H_{17}O_3NS$ (315.39).

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References

1 J. Tierney, L.M. Mascavage, D.Sheridan, D. Gorbecheva, M. Ripp, S. Son, Heterocyclic Comm., **11**, 215 (2005).

2 J. Tierney, L.M. Mascavage, M. McCoy, G. Houghton, K. Sanford, A. Findeisen, J. Kilburn, Magn. Reson. Chem., **34**, 573 (1996)

3 J. Tierney, L.M. Mascavage, A. Lagalante, N. Colasante, J. Eagles, S. Kelly, G. Lehmicke, O. Lucas, C. Mannikarottu, M. D. Nguyen, V. Rai, J. Tsai, Heterocyclic Comm., **13**, 225 (2007)

4 J. Tierney, R. Issac, L.M. Mascavage, A. Findeisen, Heterocyclic Comm., **2**, 227 (1996)

5 G. Eng, J. Tierney, D.Whalen, P. Musingarimi, M. De Rosa, Appl. Organometal. Chem., **12**, 25 (1998)
6 A. Bolognese, G. Correale, M. Manfra, A. Lavecchia, E. Novellino, V. Barone, V, Org. Biomol. **2**, 2809 (2004)
7 A. R. Surrey, J. Am Chem. Soc., **69**, 2911 (1947)
8. F. C. Brown, Chem. Rev., **61**, 463 (1961)

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