

SYNTHESIS OF 2,5-DISUBSTITUTED 3-(4-CHLOROBENZOYL)-2,3-DIHYDRO-2-METHYL-1,3,4-THIADIAZOLE DERIVATIVES

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Abstract — 2-Substituted 3-(4-chlorobenzoyl)-2,3-dihydro-5-methylthio-1,3,4-thiadiazoles (**3**) were used as key intermediates to prepare 2,5-disubstituted 3-(4-chlorobenzoyl)-2,3-dihydro-1,3,4-thiadiazoles (**4**) and (**7**).

We have previously reported that the reaction of aldehyde thiosemicarbazones and aldehyde methylthio(thiocarbonyl)hydrazones with acid chlorides gave 3-acyl-5-(acylamino)-2,3-dihydro-1,3,4-thiadiazoles¹ and 3-acetyl-2,3-dihydro-5-methylthio-1,3,4-thiadiazole,² respectively. We have also reported that nucleophilic substitution of the methylsulfinyl group of 3-acetyl-5-methylsulfinyl-2-phenyl-2,3-dihydro-1,3,4-thiadiazole gave 5-substituted 3-acetyl-2-phenyl-2,3-dihydro-1,3,4-thiadiazoles.³

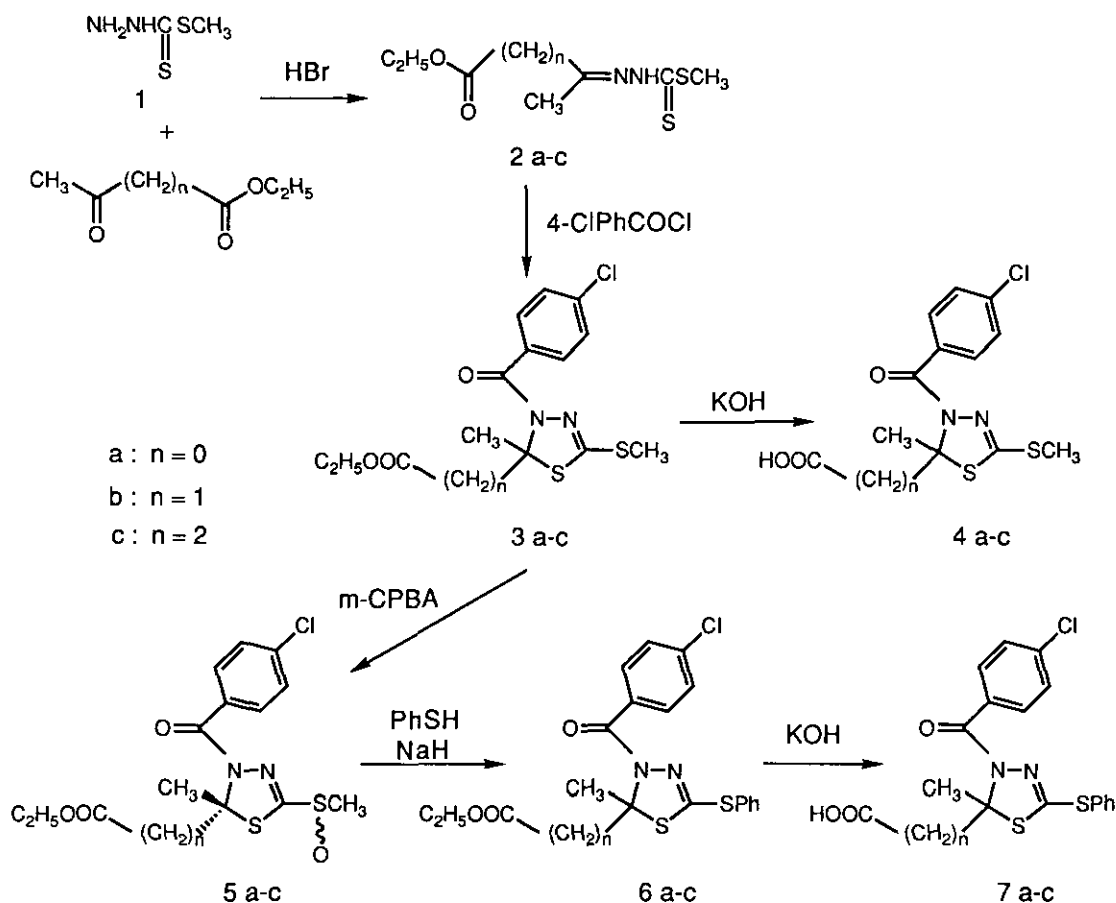
We now report the application of these methods for the synthesis of novel 2,3-dihydro-1,3,4-thiadiazole derivatives.

This paper describes the synthesis of 2,5-disubstituted 3-(4-chlorobenzoyl)-2,3-dihydro-2-methyl-1,3,4-thiadiazoles (**4a-c**) and (**7a-c**).

The synthesis of compounds (**4a-c**) and (**7a-c**) was achieved by starting with the key compounds (**3a-c**). These were prepared by the reaction of 4-chlorobenzoyl chloride with the hydrazones (**2a-c**) obtained by the condensation of methylthio(thiocarbonyl)hydrazide (**1**) with ethyl pyruvate, ethyl acetoacetate, and ethyl levulinate, respectively.

Structure proof of **3a-c** was based upon satisfactory spectral data. In addition to correct molecular formula obtained by high-resolution mass spectrometry, the ¹³C-nmr spectra clearly showed a

signal at 80.62-86.28 ppm which is assigned to the quaternary carbon in the 2,3-dihydro-1,3,4-thiadiazole ring.⁴



The first series of target compounds (**4a-c**) were then obtained by hydrolysis of **3a-c** with potassium hydroxide in aqueous methanol at room temperature. The second series (**7a-c**) were synthesized as shown in the Scheme. Starting with **3a-c**, 2,3-dihydro-5-methylsulfinyl-1,3,4-thiadiazoles (**5a-c**) were obtained by oxidation with 1.1 mol eq. of *m*-chloroperbenzoic acid (*m*-CPBA) at room temperature as diastereoisomeric mixtures in the ratio of 3:2. This ratio was determined by ¹H-nmr spectroscopy measuring the integrated intensities of the C-2 methyl signals at δ 2.20-2.32 ppm. Repeated attempts to obtain pure isomers by column chromatography were unsuccessful.

Nucleophilic substitution reactions of the diastereoisomeric mixture (**5a-c**) were examined, since the sulfinyl group is known to be a good leaving group.^{3,5,6} Treatment of diastereomeric **5a-c** with thiophenol in tetrahydrofuran (THF) in the presence of sodium hydride at room temperature for 10 min gave the corresponding 5-phenylthio derivatives (**6a-c**) in moderate yields. These were hydrolyzed with potassium hydroxide in aqueous methanol to give the target carboxylic acids (**7a-c**).

The analytical and spectral data of compounds (**6a-c**), (**4a-c**) and (**7a-c**) are shown in Tables III and IV, respectively.

EXPERIMENTAL

Melting points were determined by the capillary method and are uncorrected. Ir spectra were recorded on a Hitachi 215 spectrophotometer. ¹H-Nmr spectra were measured with a JEOL JNM-PMX 60S₁ spectrometer and ¹³C-nmr spectra with a JEOL JMS FX-200 spectrometer using tetramethylsilane as an internal reference. Mass spectra were recorded on a JEOL D-300 instrument. Column chromatography was performed on silica gel (K-100-S, from Katayama Chemicals).

Ethyl pyruvate methylthio(thiocarbonyl)hydrazone (**2a**)

Compound (**2a**) was prepared by literature method.⁷

Ethyl acetoacetate methylthio(thiocarbonyl)hydrazone (**2b**)

Compound (**2b**) was prepared by literature method.⁸

Ethyl levulinate methylthio(thiocarbonyl)hydrazone (**2c**)

A mixture of **1** (3.38 g, 27.70 mmol), ethyl levulinate (3.94 ml, 27.77 mmol), and 47 % hydrobromic acid (1 drop) in EtOH (60 ml) was stirred at room temperature for 1.5 h. The resulting precipitate was collected by filtration and recrystallized from EtOH to give **2c** (4.27 g, 62 %); mp 99-100 °C. Ir(KBr) 3220 (NH), 1725 (CO) cm⁻¹. ¹H-Nmr(CDCl₃) δ 1.32 (3H, t, *J*=7 Hz, CH₂CH₃), 2.00 (3H, s, CH₃), 2.65 (3H, s, SCH₃), 2.74 (4H, s, CH₂CH₂), 4.22 (2H, q, *J*=7 Hz, CH₂CH₃), 9.89 (1H, br s, NH). Ms *m/z* 248 (M⁺). Anal. Calcd for C₉H₁₆N₂O₂S₂: C,43.52; H,6.49; N,11.28. Found: C,43.42; H,6.56; N,11.29.

Reaction of 2a-c with 4-Chlorobenzoyl Chloride

A solution of 4-chlorobenzoyl chloride (0.58 ml, 4.56 mmol) in CHCl_3 (4 ml) was added to a stirred solution of **2a** (500 mg, 2.27 mmol) in CHCl_3 (20 ml) at room temperature. After being refluxed for 4 h, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel to give 3-(4-chlorobenzoyl)-2-ethoxycarbonyl-2,3-dihydro-2-methyl-5-methylthio-1,3,4-thiadiazole **3a** (679 mg, 83 %) as an oil. 2-Substituted 3-(4-chlorobenzoyl)-2,3-dihydro-2-methyl-5-methylthio-1,3,4-thiadiazoles (**3b**) and (**3c**) were prepared in a similar manner to that described for compound (**3a**). Yields and analytical and spectral data for compounds (**3a-c**) are given in Tables I and II.

Hydrolysis of 3a-c

A solution of 85 % KOH (899 mg, 13.62 mmol) in water (20 ml) was added to a stirred solution of **3a** (1.63 g, 4.55 mmol) in MeOH (50 ml) at room temperature. After being stirred for 6 h, the mixture was acidified with 10 % HCl, and extracted with ethyl acetate. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 , and evaporated under reduced pressure. The residue was recrystallized from isopropyl ether to give 3-(4-chlorobenzoyl)-2,3-dihydro-2-hydroxycarbonyl-2-methyl-5-methylthio-1,3,4-thiadiazole **4a** (1.29 g, 86 %). 2-Substituted 3-(4-chlorobenzoyl)-2,3-dihydro-2-methyl-5-methylthio-1,3,4-thiadiazoles (**4b**) and (**4c**) were prepared in a similar manner to that described for compound (**4a**). Yields, melting points, recrystallization solvents, and analytical and spectral data for compounds (**4a-c**) are given in Table IV.

3-(4-Chlorobenzoyl)-2-ethoxycarbonyl-2,3-dihydro-2-methyl-5-methylsulfinyl-1,3,4-thiadiazole (**5a**)

A solution of 80 % *m*-CPBA (1.08 g, 5.01 mmol) in CHCl_3 (25 ml) was added dropwise to a stirred solution of **3a** (1.63 g, 4.55 mmol) in CHCl_3 (30 ml) at room temperature. After being stirred at room temperature for 1 h, the mixture was neutralized with 5 % aqueous sodium hydrogen carbonate and extracted with CHCl_3 . The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 , and evaporated under reduced pressure. The residue was chromatographed on a silica gel column to give 2,3-dihydro-1,3,4-thiadiazole (**5a**) as an inseparable diastereomeric mixture (1.47 g, 86 %). $\text{Ir}(\text{neat})$ 1750, 1740, 1665, 1655 (CO), 1090, 1070 (SO) cm^{-1} . Major isomer; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 1.31 (3H, t, $J=7$ Hz, CH_2CH_3), 2.27 (3H, s, CH_3), 2.97 (3H, s, SOCH_3), 4.39 (2H, q, $J=7$ Hz, CH_2CH_3), 7.38 (2H, dd, $J=3, 9$ Hz, ArH), 7.73 (2H, dd, $J=3, 9$ Hz, ArH). Minor isomer; ^1H -

$\text{nmr}(\text{CDCl}_3)$ δ 1.31 (3H, t, $J=7$ Hz, CH_2CH_3), 2.32 (3H, s, CH_3), 2.93 (3H, s, SOCH_3), 4.39 (2H, q, $J=7$ Hz, CH_2CH_3), 7.38 (2H, dd, $J=3, 9$ Hz, ArH), 7.73 (2H, dd, $J=3, 9$ Hz, ArH). Ms m/z 374, 376 (M^+). Calcd for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_4\text{ClS}_2$ 374.0161, Found 374.0148.

3-(4-Chlorobenzoyl)-2-ethoxycarbonylmethyl-2,3-dihydro-2-methyl-5-methylsulfinyl-1,3,4-thiadiazole (5b)

Compound (5b) was prepared from 3b (1.26 g, 3.38 mmol) and 80 % *m*-CPBA (800 mg, 3.71 mmol) in a similar manner to that described for compound (5a). Yield 1.15 g (88 %). Ir(neat) 1735, 1725, 1665, 1655 (CO), 1090, 1075 (SO) cm^{-1} . Major isomer; $^1\text{H-nmr}(\text{CDCl}_3)$ δ 1.28 (3H, t, $J=7$ Hz, CH_2CH_3), 2.21 (3H, s, CH_3), 2.90 (3H, s, SOCH_3), 3.63 (2H, d, $J=9$ Hz, CH_2), 4.20 (2H, q, $J=7$ Hz, CH_2CH_3), 7.32 (2H, dd, $J=3, 9$ Hz, ArH), 7.62 (2H, dd, $J=3, 9$ Hz, ArH). Minor isomer; $^1\text{H-nmr}(\text{CDCl}_3)$ δ 1.28 (3H, t, $J=7$ Hz, CH_2CH_3), 2.25 (3H, s, CH_3), 2.90 (3H, s, SOCH_3), 3.61 (2H, d, $J=7$ Hz, CH_2), 4.17 (2H, q, $J=7$ Hz, CH_2CH_3), 7.32 (2H, dd, $J=3, 9$ Hz, ArH), 7.62 (2H, dd, $J=3, 9$ Hz, ArH). Ms m/z 388, 390 (M^+). Calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_4\text{ClS}_2$ 388.0324, Found 388.0298.

3-(4-Chlorobenzoyl)-2-ethoxycarbonylethyl-2,3-dihydro-2-methyl-5-methylsulfinyl-1,3,4-thiadiazole (5c)

Compound (5c) was prepared from 3c (2.22 g, 5.74 mmol) and 80 % *m*-CPBA (1.36 g, 6.30 mmol) in a similar manner to that described for compound (5a). Yield 2.07 g (90 %). Ir(neat) 1740, 1730, 1665, 1660 (CO), 1090, 1075 (SO) cm^{-1} . Major isomer; $^1\text{H-nmr}(\text{CDCl}_3)$ δ 1.26 (3H, t, $J=7$ Hz, CH_2CH_3), 2.26 (3H, s, CH_3), 2.92 (3H, s, SOCH_3), 1.90-3.54 (4H, m, CH_2CH_2), 4.20 (2H, q, $J=7$ Hz, CH_2CH_3), 7.39 (2H, dd, $J=3, 9$ Hz, ArH), 7.70 (2H, dd, $J=3, 9$ Hz, ArH). Minor isomer; $^1\text{H-nmr}(\text{CDCl}_3)$ δ 1.26 (3H, t, $J=7$ Hz, CH_2CH_3), 2.20 (3H, s, CH_3), 2.92 (3H, s, SOCH_3), 1.90-3.54 (4H, m, CH_2CH_2), 4.20 (2H, q, $J=7$ Hz, CH_2CH_3), 7.39 (2H, dd, $J=3, 9$ Hz, ArH), 7.70 (2H, dd, $J=3, 9$ Hz, ArH). Ms m/z 402, 404 (M^+). Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_4\text{ClS}_2$ 402.0475, Found 402.0447.

Reaction of 5a-c with Thiophenol in the Presence of Sodium Hydride

A suspension of sodium hydride (178 mg, 4.45 mmol, 60 % dispersion in oil, washed with ether) in anhydrous THF (10 ml) was added dropwise to a stirred solution of thiophenol (0.46 ml, 4.48 mmol) in anhydrous THF (10 ml) at 0 °C. After being stirred at room temperature for 10 min, the mixture was treated dropwise with a solution of 5a (1.67 g, 4.46 mmol) in anhydrous THF (30 ml). After 1 h at room temperature, the mixture was neutralized with aqueous acetic acid and extracted with CHCl_3 . The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 , and

evaporated under reduced pressure. The residue was chromatographed on a silica gel column to give 3-(4-chlorobenzoyl)-2-ethoxycarbonyl-2,3-dihydro-2-methyl-5-phenylthio-1,3,4-thiadiazole (**6a**) (1.25 g, 67 %) as an oil. 2-Substituted 3-(4-chlorobenzoyl)-2,3-dihydro-2-methyl-5-phenylthio-1,3,4-thiadiazoles (**6b**) and (**6c**) were prepared in a similar manner to that described for compound (**6a**). Yields and analytical and spectral data for compounds (**6a-c**) are given in Table III.

Hydrolysis of 6a-c

3-(4-Chlorobenzoyl)-2,3-dihydro-2-hydroxycarbonyl-2-methyl-5-phenylthio-1,3,4-thiadiazole (**7a**) was prepared from **6a** (1.12 g, 2.66 mmol) and 85 % KOH (528 mg, 8.00 mmol) in a similar manner to that described for compound (**4a**). Yield 764 mg (73 %). 2-Substituted 3-(4-chlorobenzoyl)-2,3-dihydro-2-methyl-5-phenylthio-1,3,4-thiadiazoles (**7b**) and (**7c**) were prepared in a similar manner to that described for compound (**4a**). Yields, melting points, recrystallization solvents, and analytical and spectral data for compounds (**7a-c**) are given in Table IV.

Table I. Spectral data for **3a-c**

Compd No.	Yield (%)	Ir cm ⁻¹ (neat) CO	Formula	Analysis ^a Calcd(Found)	Ms m/z (M ⁺)
3a	83	1740 1645	C ₁₄ H ₁₅ N ₂ O ₃ ClS ₂	358.0212 (358.0201)	358 360
3b	84	1730 1645	C ₁₅ H ₁₇ N ₂ O ₃ ClS ₂	372.0369 (372.0386)	372 374
3c	98	1730 1640	C ₁₆ H ₁₉ N ₂ O ₃ ClS ₂	386.0526 (386.0495)	386 388

^a Determined by high-resolution mass spectrometry. Upper figure, Calcd for M⁺; lower figure found.

Table II. ¹H-Nmr and ¹³C-nmr spectral data for **3a-c**.

Compd No.	¹ H-Nmr (CDCl ₃) δ (J=Hz)	¹³ C-Nmr (CDCl ₃) δ
3a	1.32(3H,t,J=7,CH ₂ CH ₃), 2.25(3H,s,CH ₃), 2.53(3H,s,SCH ₃), 4.32(2H,q,J=7,CH ₂ CH ₃), 7.35(2H,dd,J=3,9,ArH), 7.83(2H,dd,J=3,9,ArH)	13.99(q,CH ₂ CH ₃), 15.62(q,SCH ₃), 24.73(q,CH ₃), 62.60(t,CH ₂ CH ₃), 80.62(s,C-2), 127.80(d), 131.08(d), 132.56(s), 137.32(s)(aromatic C), 148.13(s,C-5), 165.59(s,CO), 168.27(s,CO)
3b	1.26(3H,t,J=7,CH ₂ CH ₃), 2.19(3H,s,CH ₃), 2.44(3H,s,SCH ₃), 3.67(2H,d,J=8,CH ₂), 4.21(2H,q,J=7,CH ₂ CH ₃), 7.35(2H,dd,J=3,9,ArH), 7.74(2H,dd,J=3,9,ArH)	14.10(q,CH ₂ CH ₃), 15.21(q,SCH ₃), 27.48(q,CH ₃), 44.09(t,CH ₂), 60.91(t,CH ₂ CH ₃), 82.20(s,C-2), 127.60(d), 130.81(d), 134.23(s), 136.71(s)(aromatic C), 149.94(s,C-5), 166.44(s,CO), 169.71(s,CO)

Table II (Continued). $^1\text{H-Nmr}$ and $^{13}\text{C-nmr}$ spectral data for **3a-c**.

Compd No.	$^1\text{H-Nmr}$ (CDCl_3) δ ($J=\text{Hz}$)	$^{13}\text{C-Nmr}$ (CDCl_3) δ
3c	1.26(3H,t, $J=7$, CH_2CH_3), 2.19(3H,s, CH_3), 2.45(3H,s, SCH_3), 2.23-3.45(4H,m, CH_2CH_2), 4.20(2H,q, $J=7$, CH_2CH_3), 7.37(2H,dd, $J=3,9$,ArH), 7.75(2H,dd, $J=3,9$,ArH)	14.16(q, CH_2CH_3), 15.24(q, SCH_3), 28.18(q, CH_3), 30.37(t, CH_2CH_2), 34.37(t, CH_2CH_2), 60.56(t, CH_2CH_3), 86.28(s,C-2), 127.60(d), 130.84(d), 134.05(s), 136.74(s)(aromatic C), 148.45(s,C-5), 166.03(s,CO), 172.10(s,CO)

Table III. Spectral data for **6a-c**.

Compd No.	Yield (%)	Ir cm^{-1} (neat) CO	$^1\text{H-Nmr}$ (CDCl_3) δ ($J=\text{Hz}$)	Formula	Analysis ^a Calcd(Found)	Ms m/z (M^+)
6a	67	1755 1660	1.33(3H,t, $J=7$, CH_2CH_3), 2.19(3H,s, CH_3), 4.33(2H,q, $J=7$, CH_2CH_3), 7.34(2H,dd, $J=3,9$,ArH), 7.82(2H,dd, $J=3,9$,ArH), 7.24-7.98(5H,m,ArH)	$\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_3\text{ClS}_2$	420.0369 (420.0367)	420 422
6b	57	1735 1650	1.24(3H,t, $J=7$, CH_2CH_3), 2.15(3H,s, CH_3), 3.66(2H,d, $J=6$, CH_2), 4.21(2H,q, $J=7$, CH_2CH_3), 7.19-7.70(9H,m,ArH)	$\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_3\text{ClS}_2$	434.0526 (434.0548)	434 436
6c	82	1740 1655	1.22(3H,t, $J=7$, CH_2CH_3), 2.09(3H,s, CH_3), 2.04-3.33(4H,m, CH_2CH_2), 4.15(2H,q, $J=7$, CH_2CH_3), 7.08-7.85(9H,m,ArH)	$\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_3\text{ClS}_2$	448.0682 (448.0686)	448 450

^a Determined by high-resolution mass spectrometry. Upper figure, Calcd for M^+ ; lower figure found.

Table IV. Spectral data for **4a-c** and **7a-c**.

Compd No.	Yield (%)	mp(°C) (a)	Ir cm^{-1} (KBr)		$^1\text{H-Nmr}$ (DMSO-d_6) δ ($J=\text{Hz}$)	Formula	Analysis			Ms m/z (M^+)
			OH	CO			Calcd	Found	C	
4a	86	161-163 (isopropyl ether)	3100-2600	1750 1605	2.14(3H,s, CH_3), 2.53(3H,s, SCH_3), 7.49(2H,dd, $J=3,9$,ArH), 7.80(2H,dd, $J=3,9$,ArH), 11.00-14.00(1H,br s,COOH)	$\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3\text{ClS}_2$	43.57 (43.73)	3.35 3.38	8.47 8.33	330 332
4b	47	137-139 (50%MeOH)	3100-2600	1710 1645	2.07(3H,s, CH_3), 2.46(3H,s, SCH_3), 3.67(2H,d, $J=8$, CH_2), 7.51(2H,dd, $J=3,9$,ArH), 7.76(2H,dd, $J=3,9$,ArH), 10.00-12.50(1H,br s,COOH)	$\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_3\text{ClS}_2$	45.28 (45.32)	3.80 3.80	8.12 8.11	344 346
4c	76	142-143 (50%EtOH)	3200-2500	1710 1640	2.14(3H,s, CH_3), 2.48(3H,s, SCH_3), 2.25-3.12(4H,m, CH_2CH_2), 7.50(2H,dd, $J=3,9$,ArH), 7.77(2H,dd, $J=3,9$,ArH), 12.40(1H,br s,COOH)	$\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_3\text{ClS}_2$	46.86 (46.87)	4.21 4.11	7.81 7.72	358 360

^a Solvent of recrystallization

Table IV(Continued). Spectral data for 4a-c and 7a-c.

Compd No.	Yield (%)	mp(°C) (a)	I _r cm ⁻¹ (KBr)		¹ H-Nmr (DMSO-d ₆)δ (J=Hz)	Formula	Analysis Calcd(Found)			Ms m/z (M ⁺)
			OH	CO			C	H	N	
7a	73	165-166 (50%EtOH)	3100-2600	1755 1600	2.11(3H,s,CH ₃),7.45(2H,dd, J=3,9,ArH),7.72(2H,dd, J=3,9,ArH),7.45-7.75(5H,m, ArH),9.50-13.50(1H,br s, COOH)	C ₁₇ H ₁₃ N ₂ O ₃ ClS ₂	51.97 (52.08)	3.34 (3.16)	7.13 (7.11)	392 394
7b	60	134-136 (50%EtOH)	3100-2600	1725 1610	2.03(3H,s,CH ₃),3.58(2H,d, J=6,CH ₂),7.33-7.69(7H,m, ArH),7.96(2H,dd, J=3,9,ArH), 10.00-12.50(1H,br s,COOH)	C ₁₈ H ₁₅ N ₂ O ₃ ClS ₂	51.13 (52.18)	3.72 (3.59)	6.88 (6.84)	406 408
7c	41		3200-2600	1710 ^b 1640	2.06(3H,s,CH ₃),1.91-2.90 (4H,m,CH ₂ CH ₂),7.28-7.82 (9H,m,ArH),10.50-13.00(1H, br s,COOH)	C ₁₉ H ₁₇ N ₂ O ₃ ClS ₂	420.0369 ^c (420.0365)			420 422

^a Solvent of recrystallization^b Neat^c Determined by high-resolution mass spectrometry. Upper figure, Calcd for M⁺; lower figure found.

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