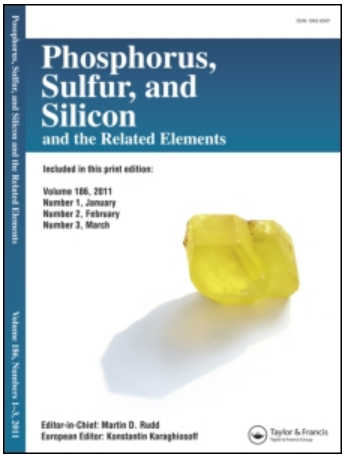

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Novel Communication: Some Novel Organosulfur Amino Acid Derivatives as Potential Antiparasitic Agents

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Novel Communication: Some Novel Organosulfur Amino Acid Derivatives as Potential Antiparasitic Agents

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The chalones **1**, **14**, *and* **26** *reacted with chlorosulfonic acid to give corresponding sulfonyl chlorides* **2**, **15**, *and* **27**, *which condensed with nucleophiles to give amino acid derivatives* **3–6**, **16–18**, *and* **28–31**. *Some of the corresponding methyl esters* **7**, **8**, **19–20**, *and* **32–34** *were prepared. Hydrazinolysis of these methyl esters yielded hydrazides* **9**, **10**, **21**, **22**, *and* **35–36**. *Coupling reaction of some amino acid derivatives with amino acid methyl ester hydrochloride in* **THF**-$\mathbf{Et_3N}$ *using dicyclohexylcarbodiimide method furnished the desired dipeptide methyl ester's* **11–13**, **23–25**, *and* **37–38**. *Some spectroscopic evidence including NMR spectra analysis are briefly discussed.*

Keywords Chalones amino acid derivatives; chlorosulfonation; sulfonyl chloride; reactions with nucleophiles as an essential amino acid

INTRODUCTION

The work described in this article forms part of our general program concerned with the chemistry and biological evaluation of arysulfonyl derivatives.[1–12] Chalcone derivatives are of interest as potential biocides, since some naturally occurring antibiotics,[13] and aminochalcones[14,15] owe their activity to the presence of the α,β-unsaturated carbonyl group. Chlorosulfonation provides a useful route to a variety of sulfonyl derivatives by nucleophilic displacement of the chlorine atom in the resulting sulfonyl chloride. These compounds are of interest for potential biocidal activity.[16–19]

Early workers[20] examined the sulfonation of chalcone and 4-methoxychalcone and concluded that the latter gave sulfonic acid. Later, several chalcone-4-sulfonamides were prepared by a condensation of N-substituted P-sulfonyl benzaldiacetates with substituted acetophenones.[21] In chalcones (1 and 26) the 4- or 5-position should be active due to the activating influence of the olefinic double bond.

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We have demonstrated that the optimum conditions for the chlorosulfonation of chalcone (75% yield) were by a reaction with a reagent (6 mol. equivalent); for 3 weeks at r.t., the more reactive P-methoxy chalcone reacted faster under similar conditions (63% yield in one week or 75% yield in 24 h, respectively).

DISCUSSION

The present work involves the chlorosulfonation of chalcones **1**, **14**, and **16** (Chart 1).

The chalcones were prepared by the standard procedure[22,23] involving base-catalyzed condensation of the appropriate aromatic aldehyde and accetophenone or the p-methoxy derivatives.

The different chalcones were reacted with chlorosulfonic acid, generally, 6 mol. equivalents or 3 mol. equivalents in excess thionyl chloride at r.t., to give the corresponding sulfonyl chlorides, which were condensed with a range of amino acid to give the sulfonamide listed in Table I.

Chalcones are active due to the powerful combined electron-donating methoxy group and the alkenic double bond in enhancing reactivity of the benzene ring with respect to electrophilic attack. The NMR spectra of chlacone which demonstrated that the alkenic H-proton (δ 7.79, 7.72) the most sensitive to substitutent effects.

The **NMR** spectra of 2-thienylidene sulfonylamino acid showed the resonance of thiophene protons as a doublet (δ 7.7). In chalcone PhCO.CH=CH moiety was estimated from the literature-data for PhCO and CH=CH group.[24]

The electron impact mass spectra of the majarity of the chalcone sulfonylamino acid derivatives showed the molecular ions M^+.

EXPERIMENTAL

Melting points were taken on a Griffin melting point apparatus and are uncorrected. Infrared analysis of solid samples were run as a KBr disc on a Schimadzu model 440 spectrophotometer. ^{1}H NMR spectra were measured in DMSO-d_6 as a solvent unless otherwise stated using Fx 90 Q Fourier Transform ^{1}H NMR. Mass spectra were obtained using a Schimadzu (Japan). GC. M.S. QP 1000 Ex spectrometer using the direct inlet system. TLC analyses were carried out on Merek silica gel plates and developed with n-butanol-acetic acid-water (4:1:1) using iodine, ninhydrin, and benzidine as spraying agents.

Compounds **2**, **15**, and **27** were prepared according to the procedure described earlier.[25,26]

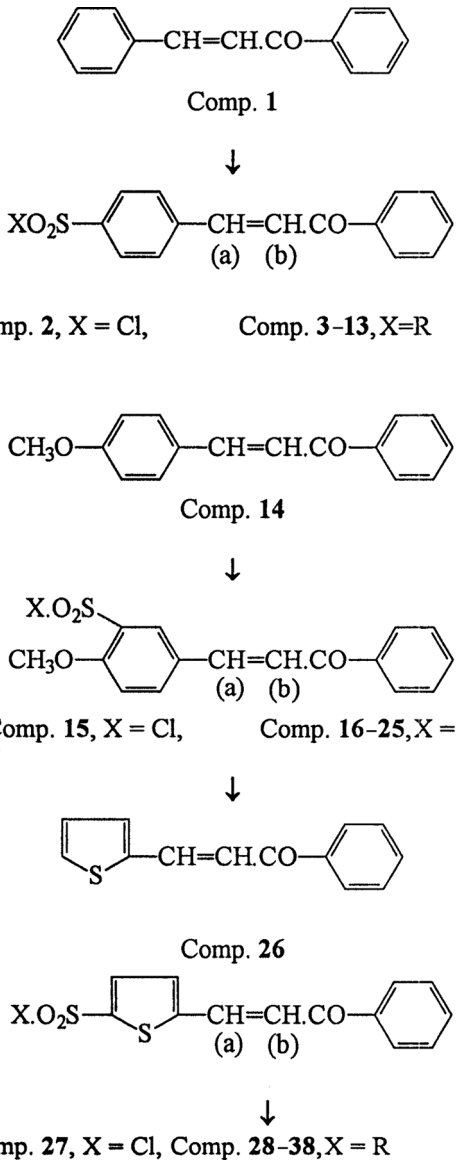

CHART 1

Coupling Reaction 3–5, 16–18, and 28–31: General Procedure

To an amino acid (0.11 mol) in a water (25 mL) THF (15 mL) mixture was added triethylamine (5 mL), followed by a protionwise addition

TABLE I Physical Data for the Chalconesulfonyl, Amino Acid Derivatives 2–13, 16–25, and 28–38

Compound No.	R	M.P. °C	Yield %	R_f	Molecular Formula	Elemental Analysis % Calculated/Found			
						% C	% H	% N	% S
3	Gly	224–226	53	0.76	$C_{17}H_{15}NO_5S$	59.13	4.35	4.06	9.28
						59.10	4.33	4.03	9.25
4	DL-Ala	264–266	64	0.73	$C_{18}H_{17}NO_5S$	60.17	4.74	3.90	9.91
						60.00	4.71	3.89	9.90
5	L-Val	230–232	70	0.80	$C_{20}H_{21}NO_5S$	62.02	5.43	3.62	8.27
						62.00	5.41	3.61	8.11
6	L-Leu	244–246	75	0.74	$C_{21}H_{23}NO_5S$	62.84	5.74	3.49	7.98
						62.80	5.71	3.41	7.96
7	L-Val-OMe	266–268	76	0.84	$C_{21}H_{23}NO_5S$	62.84	5.79	3.49	7.98
						62.84	5.73	3.45	7.96
8	L-Leu-OMe	268–270	79	0.77	$C_{22}H_{25}NO_5S$	63.61	6.02	3.37	7.71
						63.60	6.00	3.33	7.70
9	L-Val-N_2H_3	248–250	63	0.71	$C_{20}H_{23}N_3O_4S$	59.85	5.74	10.47	7.98
						59.81	5.73	10.41	7.93
10	L-Leu-N_2H_3	259–261	66	0.77	$C_{21}H_{25}N_3O_4S$	60.72	6.02	10.12	7.71
						60.70	6.00	10.00	7.00
11	Gly-Gly-OMe	278–280	65	0.85	$C_{20}H_{20}N_2O_6S$	57.69	4.81	6.73	7.69
						57.00	4.80	6.71	7.66
12	DL-Ala-Gly-OMe	255–257	77	0.94	$C_{21}H_{22}N_2O_6S$	58.60	5.12	6.51	7.44
						58.58	5.10	6.48	7.41
13	L-Leuc-Gly-OMe	280–282	70	0.90	$C_{24}H_{28}N_2O_6S$	61.02	5.93	5.93	6.79
						61.00	5.90	5.91	6.73
16	DL-Ala	209–211	55	0.61	$C_{19}H_{19}NO_6S$	58.61	4.88	3.60	8.23
						58.58	4.83	3.50	8.19

17	L-Val	212–214	50	0.63	$C_{21}H_{23}NO_6S$	60.43	5.52	3.36	7.67
						60.40	5.48	3.30	7.61
18		L-Leu 194–196	60	0.77	$C_{22}H_{25}NO_6S$	61.25	5.80	3.25	7.42
						61.21	5.76	3.18	7.33
19	L-Val-OMe	214–216	66	0.80	$C_{22}H_{25}NO_6S$	61.25	5.80	3.25	7.42
						61.19	5.77	3.16	7.38
20	L-Leu-OMe	196–198	67	0.84	$C_{23}H_{27}NO_6S$	62.02	6.07	3.15	7.19
						62.00	6.00	3.00	7.00
21	L-Val-N_2H_3	222–224	71	0.76	$C_{21}H_{25}N_3O_5S$	58.47	5.80	9.74	7.42
						58.41	5.77	9.71	7.38
22	L-Leu-N_2H_3	230–232	69	0.74	$C_{22}H_{27}N_3O_5S$	59.32	6.07	9.44	7.19
						59.30	6.00	9.33	7.00
23	DL-Ala-Gly-OMe	170–172	58	0.98	$C_{22}H_{24}N_2O_7S$	57.39	5.22	6.09	6.96
						57.33	5.20	6.00	6.81
24	L-Val-Gly-OMe	148–150	52	0.92	$C_{24}H_{28}N_2O_7S$	59.02	5.74	5.74	6.56
						59.00	5.61	5.62	6.44
25	L-Leu-Gly-OMe	162–164	88	0.75	$C_{25}H_{30}N_2O_7S$	59.76	5.98	5.58	6.37
						59.66	5.91	5.53	6.30
28	DL-Ala	170–172	59	0.81	$C_{16}H_{15}NO_5S_2$	52.60	4.11	3.83	17.53
						52.55	4.00	3.81	17.51
29	L-Val	151–153	49	0.78	$C_{18}H_{19}NO_5S_2$	54.96	4.83	3.56	16.23
						54.91	4.81	3.52	16.28
30	L-Leu	162–164	58	0.76	$C_{19}H_{21}NO_5S_2$	56.02	5.16	3.44	15.72
						56.00	5.00	3.41	15.70

(*Continued on next page*)

TABLE I Physical Data for the Chalconesulfonyl, Amino Acid Derivatives 2–13, 16–25, and 28–38 (*Continued*)

Compound No.	R	M.P. °C	Yield %	R_f	Molecular Formula	Elemental Analysis % Calculated/Found			
						% C	% H	% N	% S
31	N-Et_2	94–96	53	0.61	$C_{17}H_{17}NO_3S_2$	58.45	5.44	4.01	18.34
						58.41	5.42	4.00	18.34
32	DL-Ala-OMe	109–111	53	0.77	$C_{17}H_{17}NO_5S_2$	53.82	4.49	3.69	16.89
						53.80	4.44	3.63	16.81
33	L-Val-OMe	117–119	50	0.71	$C_{19}H_{21}NO_5S_2$	56.02	5.16	3.44	15.72
						56.00	5.10	3.41	15.70
34	L-Leu-OMe	129–131	56	0.77	$C_{20}H_{33}NO_5S_2$	57.01	5.46	3.33	15.20
						57.00	5.41	3.30	15.00
35	L-Val-N_2H_3	100–102	69	0.75	$C_{18}H_{21}N_3O_4S_2$	53.07	5.16	10.32	15.72
						53.00	5.11	10.31	15.71
36	L-Leu-N_2H_3	112–114	71	0.80	$C_{19}H_{23}N_3O_4S_2$	54.16	5.46	9.98	15.20
						54.00	5.41	9.91	15.13
37	L-Val-Gly-OMe	208–210	62	0.84	$C_{21}H_{24}N_2O_6S_2$	54.31	5.17	6.03	13.79
						54.31	5.11	6.00	13.71
38	L-Leu-Gly-OMe	200–202	79	0.87	$C_{22}H_{26}N_2O_6S_2$	55.23	5.44	5.86	13.39
						55.21	5.41	5.81	13.33

of sulfonyl chlorides (0.1 mol) during 30 min. The temperature of the reaction mixture during the process of the addition was kept at 10°C. Stirring continued for 4 h at 20°C. Tetrahydrofuran was removed by concentration of the reaction mixture under reduced pressure. Water (50 mL) was then added and acidified with 2M HC1 to pH5. The crude products were filtered and recrystallized (ethanol-water). All of products **3–5**, **16–18**, and **28–31** were chromatographicallv homogeneous by iodine and benzidine development in TLC, Table I and Chart 1.

IR of 4: ν3400 cm^{-1} (NH), ν1690 cm^{-1} (CO), ν1420, 1360 cm^{-1} (SO_2-NH), ν1600 cm^{-1} (Ar-C=C), ν1320, 1160 cm^{-1} (SO_2)

IR of 17: ν1680 cm^{-1} (CO), ν1600 cm^{-1} (Ar-C=C), ν1320, 1180 cm^{-1} (SO_2)

IR of 30: ν3200 cm^{-1} (NH), ν1680 cm^{-1} (CO), ν1610 cm^{-1} (Ar-C=C), ν1350, 1160 cm^{-1} (SO_2)

^{1}H NMR of 4: (DMSO-d_6): δ1.1–1.2 (s, 3H, $\underline{CH_3}$), δ4.2–4.6 (s, αH, $\underline{CH}$), δ4.7–5.2 (s, H, $\underline{NH}$), δ7.8–7.7 (9H, ArH), δ8.1, 7.4 (alkenic H_a, H_b), δ10.9 (s, H, COOH). **MS of 4:** m/z 359 (M^+)

^{1}H NMR of 17: (DMSO-d_6): δ0.9[s, 6H, $(\underline{CH_3})_2$], δ1.97 (s, H, β $\underline{CH}$), δ4.26 (s, H, $\alpha\underline{CH}$), δ3.97 (s, 3H, O—CH_3), δ4.8–5.2 (s, H, $\underline{NH}$), δ8.30–7.03 (10H, ArH and alkenic H_a, H_b), (H_a) 7.79, 7.72, (H_b) 7.53, 7.49, δ10.9 (s, H, COOH). **MS of 17:** m/z 417 (M^+)

^{1}H NMR of 30: (DMSO-d_6): δ0.9[s, 6H, $(CH_3)_2$], δ4.5(s, 2H, $\underline{CH_2}$), δ8.4–7.5 (9H, ArH), and alkenic H_a, H_b, δ9.8 (s, H, COOH), δ10.49 (s, H, SO_2NH). **MS of 30:** m/z 407 (M^+)

^{1}H NMR of 31: (DMSO-d_6): δ 0.9[s, 6H, $(CH_3)_2$], δ8.5–7.5(9H, ArH and CH=CH), δH_a, 7.72, δH_b 7.53, δ7.7 (s, 2H, thiophene 3,4-H), δ3.4–3.2 (4H, N · CH_2 · $\underline{CH_3}$), δ1.3–1.15(6H, N-CH_2-$\underline{CH_3}$). **MS of 31:** 349 (M^+), 277 (M-NEt_2), signals removed by D_2O tratment 213 (M-SO_2-NEt2).

Synthesis of Chalcone Sulfonylamino Acid Methyl Esters 7–8, 19–20, and 33–34: General Procedure

A suspension of coupling reaction products **5–6**, **17**, **18 28**, and **30** (0.2 mole) in absolute methanol (100 mL) was cooled to −10°C, and pure

thionyl chloride (2.2 mL) was added dropwise during 1 h. The reaction mixture was stirred for an additonal 3–4 h at r.t. after standing overnight, and the solvent was removed by vacuum distillation. The residual solid material was recrystallized (methanol-water). (cf., Table I, Chart 1).

IR of 8: ν3300, 3180 cm^{-1} (NH), ν1600, 1610 cm^{-1} (CO), ν1370, 1170 cm^{-1} (SO_2-NH), ν1610 cm^{-1} (ArC—C), ν1350, 1150 cm^{-1} (SO_2), ν1360 cm^{-1} ($COOCH_3$)

^{1}H NMR of 19: (DMSO-d_6): δ8.2–7.0(Ar-H and alkenic H_a, H_b), δ3.51–3.41(s, 3H, $COOCH_3$)

^{1}H NMR of 32: (DMSO-d_6): δ8.04(s, H, NH), δ3.75(s, 3H, $COOCH_3$), δ4.4(H, αCH), δ1.2(3H, βCH_3) absence of OH proton, and other peak in support of their structure

Synthesis of Chalcone Sulfonylamino Acid Hydrazides 9, 10, 19, 20, and 35, 36: General Procedure

The methyl esters **7, 8, 19, 20, 33,** and **34** (0.2 mol) were dissolved in ethanol (100 mL), and hydrazine hydrate 85% (0.2 mol) was added. The reaction mixture was stirred for 3 h at 20°C and left for 24 h at r. t. The crystalline products **19, 10, 19, 20, 35,** and **36** were filtered off, washed with water, and recrystallized (ethanol–water).

IR of 35: ν3340, 3125 cm^{-1} (NH), ν1640 cm^{-1} (CO), ν1600, 1550 cm^{-1} Ar C=C, ν1340, 1180 cm^{-1} (SO_2)

^{1}H NMR of 36: (DMSO-d_6): δ9(H, SO_2NH), δ8.2–7.5(Ar-H), δ5.50 (H, NH), δ5.61 (2H, NH_2)

Synthesis of Chalcone Sulfonylamino Dipeptide Methyl Esters 11–13, 23–25, and 37–38: General Procedure

To a solution of amino acid methyl ester hydrochloride (0.11 mol) in THF (100 mL) was added trethylamine (5 mL). The solution was stirred at 20°C for 30 min and cooled to 0°C, where the sulfonyl amino acid (0.001 mol) and dicyclohexylcarbodiimide DCC (1.62 g) were added to the mixture. The reaction mixture was stirred for 2 h at 0°C and for another 2 h at r.t. The precipitated dicyclohexylurea was filtered off, and acetic acid (2 mL) was added to the solution, which was left standing overnight. A precipitate was filtered off and the remaining solution was distilled under vacuum. The remaining solid was recrystallized (ethanol-water). The products were chromatographically homogeneous.

IR of 12: ν3300, 3100 cm^{-1} (NH, CONH), ν1750 cm^{-1} (CO), ν1320 cm^{-1} ($COOCH_3$)

^{1}H NMR of 12: (DMSO-d_6): δ7.82 (s, 2H, $SO_2\underline{NH}$), δ8.04(s, H, $CO\underline{NH}$), δ3.8(s, 3H, $COOCH_3$), δ3.65(s, 2H, $\underline{CH_2}$), δ4.32(s, H, α-$\underline{CH}$-alalyl) δ1.21(s, 3H, CH_3 alalyl) and other bands supporting the structure of dipeptide

^{1}H NMR of 37: (DMSO-d_6): δ3.84(s, 3H, $COOCH_3$), δ4.26(s, H, $\alpha\underline{CH}$ νalyl), δ 1.79(s, H, βCH-valyl), δ0.95[s, 6H, $(CH_3)_2$], δ3.65(s, 2H, CH_2) and other bands supporting the structure of dipeptide

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