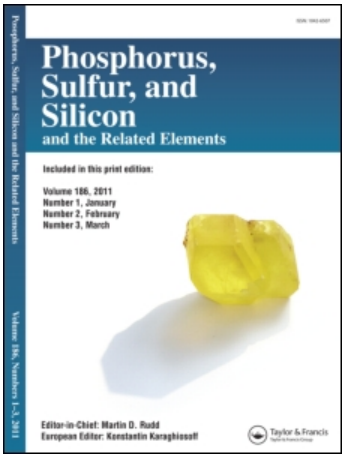


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# A FACILE SYNTHESIS AND SOME NEW REACTIONS OF N-BENZYLCARBOXAMIDES WITH ESSENTIAL AMINO ACIDS

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# A FACILE SYNTHESIS AND SOME NEW REACTIONS OF N-BENZYLCARBOXAMIDES WITH ESSENTIAL AMINO ACIDS

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N-Benzyl-p-chloro and N-Benzyl-2,4-dichlorobenzamide react with hlorosulfonic acid to give the corresponding p-sulfonyl chlorides (**1,19**), which condensed with nucleophiles to give amino acid derivatives (**2–7**) and (**20–25**). Some of the corresponding methyl esters (**8–11**) were prepared. Hydrazinolysis of these methyl esters yielded the hydrazides (**12–15**). Coupling reactions of some amino acid derivatives with amino acid methyl ester hydrochloride in THF-$Et_3N$ medium using the dicyclohexylcarbodiimide method furnishes the desired dipeptide methyl esters (**16–18, 26–28**). Some spectral data are briefly discussed.

*Keywords:* Chlorosulfonation of N-Benzyl-4-Chlorobenzamide; N-Benzyl-2,4-Dichlorobenzamide and Their Reactions with Different Essential Amino Acids

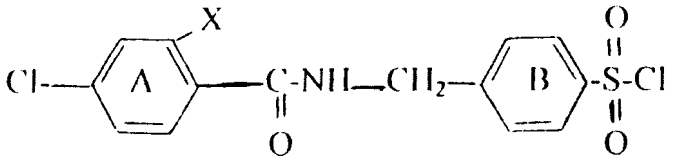
## INTRODUCTION

The work reported here is a continuation of our general program on the chemistry and reactivity of aryl sulfonyl derivatives as candidate pesticides, which are found to possess hypoglycemic, antipyretic, analgesic diuretic, bacteriostatic, and other pharmacological activities.

The compounds mentioned were found to have these activities.[1–4]

Amides and anilides[5–6] react smoothly with chlorosulfonic acid to yield the corresponding sulfonyl chlorides. The chlorosulfonation of anilides is facilitated by the electron releasing properties of the amidic nitrogen atom.

In the present work, the reaction of some benzylbenzamides with chlorosulfonic acid was studied. The orientation of sulfonation is governed by the electron releasing effect of the methylene group.



(1), x = H; (19), x = Cl

The other aromatic center is deactivated towards electrophilic substitution by the adjacent electron withdrawing carbonyl group. The sulfonyl chlorides (**1,19**) by condensation with nucleophiles e.g. amino acids residue can be converted into sulfonylamino acid derivatives for biological evaluation as candidate biocides.



## DISCUSSION

The NMR spectrum of **3** showed the resonance of the **4-protons** of the phenyl ring (A) ($\delta$ 7.7) at lower field than the multiplet due to the **4-protons** of ring (B) ($\delta$ 8.2). The difference arises from the deshielding effects of the chlorine and carbonyl groups on the ring (A) protons. The methylene protons appeared as a doublet ($\delta$ 4.6) which was in excellent agreement with the calculated value ($\delta$ 4.5) based on the application of Schoolery's Rule.

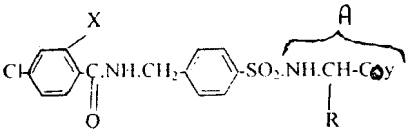
The mass spectra of N-benzylcarboxamides amino acid derivatives (**3, 6, 23**) show the fragmentation pattern which was consistent with successive loss of the $Ph.CH_2$, NH, and CO moieties.

N-Benzyl-p-chlorobenzamide reacts with chlorosulfonic acid (6 equivalent) in boiling chloroform (3h) to afford an excellent yield (84%) of the p-sulfonyl-chloride (**1**), N-benzyl-2,4-dichloro benzamide was similarly converted into (**19**); yield (74%).

The sulfonyl chlorides (**1, 19**) were condensed with different amino acids using the THF-$Et_3N$ method to give the expected sulfonyl derivatives (**2–18**), (**20–25**) (chart 1 and Table I).

The two aromatic rings A and B apparently have comparable reactivity towards sulfonation, because the electron releasing effect of the methylene group of the phenyl ring (B) would be relatively weak.

The IR spectra of the sulfonly chlorides (**1,19**) showed the normal stretching absorption associated with the C=O, NH, and Ar C=C groups and additionally two bands at 1380–1330 and 1180–1130 indicative of the $SO_2$ group.[7]



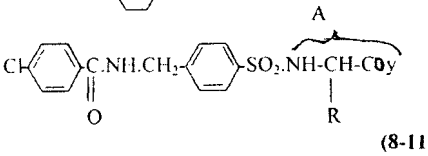
y = OH

**(2-7)**; X = H

2- R = H
3- R = $CH_3$
4- R = $CH.(CH_3)_2$
5- R = $CH.(CH_3)_2$
6- R = $CH_2.CH.(CH_3)_2$
7- R = $CH_2$-C6H4-OH

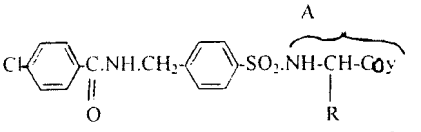
**(20-25)**; X = Cl

20- R = H
21- R = $CH_3$
22- R = $CH.(CH_3)_2$
23- R = $CH_2.CH.(CH_3)_2$
24- R = $CH_2$-C6H4-OH
25- R = $CH_2$-C6H5



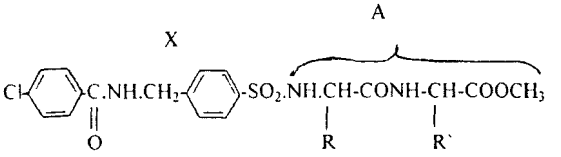
**(8-11)**; y = $OCH_3$

8- R = H
9- R = CH
10- R = $CH.(CH_3)_2$
11- R = $CH_2.CH.(CH_3)_2$



**(12-15)**; y = $N_2H_3$

12- R = H
13- R = $CH_3$
14- R = $CH.(CH_3)_2$
15- R = $CH_2.CH.(CH_3)_2$



16- X = H R = H R` = H
17- X = H R = $CH_2.CH(CH_3)_2$ R` = H
18- X = H R = $CH_2$-C6H4-OH R` = H
26- X = Cl R = H R` = H
27- X = Cl R = $CH_3$ R` = H
28- X = Cl R = $CH.(CH_3)_2$ R` = H

CHART I

TABLE I Physical data for the N-(4-sulfonylbenzyl)-4-chloro-and, 2,4-dichlorabenzamides (2–18) and (20–28).

| Comp. No. | A | m.p. °C | Yield % | $R_f$ | Molecular formula | Elemental Analysis Calculated/Found | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | %C | %H | %N | %S |
| 2 | Gly | 183–185 | 74 | 0.83 | $C_{16}H_{15}ClN_2O_5S$ | 50.20 | 3.92 | 7.32 | 8.37 |
| | | | | | | 50.18 | 3.90 | 7.30 | 8.35 |
| 3 | DL-Ala | 205–207 | 65 | 0.80 | $C_{17}H_{17}ClN_2O_5S$ | 51.45 | 4.29 | 7.06 | 8.07 |
| | | | | | | 51.43 | 4.27 | 7.04 | 8.05 |
| 4 | L-Val | 213–215 | 72 | 0.90 | $C_{19}H_{21}ClN_2O_5S$ | 53.71 | 4.95 | 6.60 | 7.54 |
| | | | | | | 53.70 | 4.93 | 6.60 | 7.50 |
| 5 | DL-Val | 198–200 | 74 | 0.88 | $C_{19}H_{21}ClN_2O_5S$ | 53.70 | 4.95 | 6.60 | 7.54 |
| | | | | | | 53.70 | 4.92 | 6.58 | 7.53 |
| 6 | L-Leu | 163–165 | 65 | 0.84 | $C_{20}H_{23}ClN_2O_5S$ | 54.73 | 5.28 | 6.38 | 7.30 |
| | | | | | | 54.73 | 5.26 | 6.36 | 7.29 |
| 7 | L-Tyr | 177–179 | 70 | 0.81 | $C_{21}H_{21}ClN_2O_5S$ | 56.50 | 4.30 | 5.37 | 6.55 |
| | | | | | | 56.50 | 4.28 | 5.36 | 6.53 |
| 8 | Gly-OMe | 170–172 | 57 | 0.90 | $C_{17}H_{17}ClN_2O_5S$ | 51.45 | 4.29 | 7.06 | 8.07 |
| | | | | | | 51.43 | 4.27 | 7.04 | 8.05 |
| 9 | DL-Ala-OMe | 138–140 | 62 | 0.85 | $C_{18}H_{19}ClN_2O_5S$ | 52.62 | 4.63 | 6.82 | 7.80 |
| | | | | | | 52.60 | 4.61 | 6.80 | 7.80 |
| 10 | L-Val-OMe | 178–180 | 65 | 0.77 | $C_{20}H_{23}ClN_2O_5S$ | 54.73 | 5.25 | 6.39 | 7.30 |
| | | | | | | 54.71 | 5.23 | 6.36 | 7.28 |
| 11 | L-Leu-OMe | 123–125 | 50 | 0.79 | $C_{21}H_{25}ClN_2O_5S$ | 55.69 | 5.52 | 6.19 | 7.07 |
| | | | | | | 55.67 | 5.50 | 6.17 | 7.05 |
| 12 | Gly-$N_2H_3$ | 160–162 | 72 | 0.90 | $C_{16}H_{17}ClN_4O_4S$ | 48.42 | 4.29 | 14.12 | 8.07 |
| | | | | | | 48.40 | 4.27 | 14.10 | 8.05 |
| 13 | DL-Ala-$N_2H_3$ | 122–124 | 88 | 0.86 | $C_{17}H_{19}ClN_4O_4S$ | 49.70 | 4.63 | 13.64 | 7.80 |
| | | | | | | 49.70 | 4.61 | 13.61 | 7.80 |
| 14 | L-Val-$N_2H_3$ | 154–156 | 78 | 0.94 | $C_{19}H_{21}ClN_4O_4S$ | 52.00 | 5.25 | 12.77 | 7.30 |
| | | | | | | 52.00 | 5.22 | 12.75 | 7.26 |
| 15 | L-Leu-$N_2H_3$ | 110–112 | 81 | 0.96 | $C_{20}H_{25}ClN_4O_4S$ | 53.04 | 5.52 | 12.38 | 7.07 |
| | | | | | | 53.01 | 5.50 | 12.35 | 7.05 |
| 16 | Gly-Gly-OMe | 133–135 | 70 | 0.76 | $C_{19}H_{20}ClN_3O_6S$ | 50.28 | 4.41 | 9.26 | 7.06 |
| | | | | | | 50.26 | 4.40 | 9.24 | 7.05 |
| 17 | L-Leu-Gly-OMe | 120–122 | 78 | 0.60 | $C_{28}H_{28}ClN_3O_6S$ | 59.00 | 4.92 | 7.37 | 5.62 |
| | | | | | | 59.00 | 4.90 | 7.35 | 5.60 |
| 18 | L-Tyr-Gly-OMe | 143–145 | 65 | 0.50 | $C_{26}H_{26}ClN_3O_7S$ | 55.76 | 5.65 | 7.51 | 5.72 |
| | | | | | | 55.75 | 5.64 | 7.50 | 5.70 |
| 20 | Gly | 93–95 | 49 | 0.83 | $C_{16}H_{14}Cl_2N_2O_5S$ | 46.04 | 3.36 | 6.71 | 7.67 |
| | | | | | | 46.01 | 3.33 | 6.69 | 7.63 |
| 21 | L-Ala | 70–72 | 41 | 0.74 | $C_{17}H_{16}Cl_2N_2O_5S$ | 47.33 | 3.71 | 6.50 | 7.42 |
| | | | | | | 47.30 | 3.70 | 6.42 | 7.40 |

TABLE I *continued*

| *Comp. No.* | *A* | *m.p. °C* | *Yield %* | $R_f$ | *Molecular formula* | *Elemental Analysis Calculated/Found* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *%C* | *%H* | *%N* | *%S* |
| 22 | L-Val | 75–77 | 39 | 0.88 | $C_{19}H_{20}Cl_2N_2O_5S$ | 49.67 | 4.36 | 6.10 | 6.97 |
| | | | | | | 49.64 | 4.33 | 6.09 | 6.94 |
| 23 | L-Leu | 72–74 | 55 | 0.75 | $C_{20}H_{22}Cl_2N_2O_5S$ | 50.74 | 4.65 | 5.92 | 6.77 |
| | | | | | | 50.11 | 4.62 | 5.90 | 6.73 |
| 24 | L-Tyr | 63–65 | 53 | 0.86 | $C_{23}H_{20}Cl_2N_2O_6S$ | 52.77 | 3.82 | 5.35 | 6.12 |
| | | | | | | 52.75 | 3.80 | 5.31 | 6.10 |
| 25 | L-Phe | 80–82 | 52 | 0.75 | $C_{23}H_{20}Cl_2N_2O_5S$ | 54.44 | 3.94 | 5.52 | 6.31 |
| | | | | | | 54.41 | 3.91 | 5.51 | 6.30 |
| 26 | Gly-Gly-OMe | 65–67 | 63 | 0.66 | $C_{19}H_{19}Cl_2N_3O_6S$ | 46.72 | 3.89 | 8.61 | 6.56 |
| | | | | | | 46.70 | 3.85 | 8.60 | 6.54 |
| 27 | L-Ala-Gly-OMe | 118–120 | 55 | 0.89 | $C_{20}H_{21}Cl_2N_3O_6S$ | 47.81 | 4.18 | 8.37 | 6.37 |
| | | | | | | 47.80 | 4.15 | 8.35 | 6.34 |
| 28 | L-Leu-Gly-OMe | 112–124 | 53 | 0.91 | $C_{23}H_{27}Cl_2N_3O_6S$ | 50.74 | 4.96 | 7.72 | 5.88 |
| | | | | | | 50.74 | 4.94 | 7.70 | 5.85 |

* Crystallisation solvent: a = Methanol-water (**2–11**), (**16–18**), (**20–25**), b = Ethanol-water (**12–15**)

All the compounds synthesized (**2–28**) give IR, NMR, mass spectra consistent with the assigned structure.

## EXPERIMENTAL

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

### N-(4-Chlorosulfonylphenyl)-4-chlorobenzamide(1), and N-(4-chlorosulfonylphenyl)-2,4-dichlorobenzamide(19)

The title compounds were prepared according to the procedure described earlier.[8]

## Coupling Reactions: (2–7, 20–25)

### General Procedure

To an amino acid (0.1 mol) in a water (25 ml) THF (15 ml) mixture, was added triethylamine (5 ml), followed by protionwise addition of the sulfonyl chlorides (0.11 mol) during 30 min. The temperature of the reaction mixture during the process of addition was kept at 10°C. Stirring continued for 2 h at 20°C. Tetrahydrofuran was removed by concentration of the reaction mixture under reduced pressure, water (30 ml) was added and acidified with 2 M HCL to $pH_5$. The crude products were filtered and recrystallized. All the products (**2–7**) and (**20–25**) were chromatographically homogeneous by iodine and benzidine development cf. Table I. Compd. (**2–7**) and (**20–25**).

**IR** of **3** :$\nu$3350 $cm^{-1}$ (NH), $\nu$1660 $cm^{-1}$ (C=O), $\nu$1600, 1580 $cm^{-1}$ (Ar C=C), $\nu$1360, 1130 $cm^{-1}$ ($SO_2$), 760 $cm^{-1}$ (C-Cl).

**IR** of **21** :$\nu$3270 $cm^{-1}$ (NH), $\nu$1640 $cm^{-1}$ (CO), $\nu$1590 $cm^{-1}$, Ar(C=C), $\nu$1350, 1150 $cm^{-1}$ ($SO_2$).

$^1$H-**NMR** of **3** :(DMSO-$d_6$): δ 1.2(3H, CH-$\underline{CH_3}$), 4.2(1H, $\underline{CH}$); 4.6(2H, $\underline{CH_2}$), 7.35 (4H; ArH(B)), 7.7 (4H, ArH(A)), 9.2($\underline{1H}$, COOH), $\underline{MS}$ of 3: m/z 397 ($M^+$).

$^1$H-**NMR** of **6** :(DMSO-$d_6$): δ 4.1(1H, $\underline{CH}$), 4.5(2H; $\underline{CH_2}$), 7.7(4H,Ar-H(B)), 8.2(4H, Ar-H(A)), 9.8($\underline{1H}$, COOH), $\underline{MS}$ of 6: m/z 439 ($M^+$).

$^1$H-**NMR** of **23** :(DMSO-$d_6$): δ 0.9(6H, $(CH_3)_2$)), 4.6(2H, $\underline{CH_2}$); (7.5–8.4) 7H Ar-H), 9.8 (1H, COOH, **MS** of 23: m/z 473 ($\underline{M^+}$).

### Synthesis of Sulfonylmino Acid Methyl Esters (8–11) General Procedure

A suspension of coupling reaction products (**2,3,4,6**) (0.01 mole) in absolute methanol (150 ml) was cooled to $-10$°C and pure thionyl chloride (1.2 ml) was added dropwise during one hour. The reaction mixture was stirred for an additional 3–4 h at room temperature. Kept overnight when the solvent was removed by vacuum distillation. The residual solid material was recrystallized, (methanol-water). (cf. Table I) (chart 1).

**IR** of **8** :$\nu$1760, 1720 $cm^{-1}$ C=O, 1730 $cm^{-1}$ ($COOCH_3$).

$^1$H-**NMR** of **9** :(DMSO-$d_6$): δ (7.6–8.4, Ar-H), 3.3(3H, $OCH_3$), and disappear of OH protons.

### Synthesis of Sulfonylmino Acid Hydrazides (12–15) General Procedure

The methyl esters (**8–11**) (0.01 mol) were dissolved in ethanol (50 ml) and hydrazine hydrate 85% (0.02 mol) was added. The reaction mixture was stirred

for 3 h at 20°C and left 24 h at room temperature. The crystalline products (**12–15**) were filtered off, washed with water and recrystallized from (ethanol-water).

The hydrazides (**12–15**) were shown to be chromoatographically to be homogeneous. (cf. Table I). (chart 1).

| | |
|---|---|
| **IR** of **12** | :$\nu$3340, 3125 $cm^{-1}$ (NH) 1640 $cm^{-1}$ (C=O), 1600, 1550 $cm^{-1}$ (Ar C=C), 1340, 1180 $cm^{-1}$ ($SO_2$), 690 $cm^{-1}$ (C-Cl). |
| $^1$H-**NMR** of **14** | :(DMSO-$d_6$): $\delta$ 9(1H, $SO_2\underline{NH}$), 8.1 (1H, $\underline{NH}.CH_2$), 8.2–7.5(Ar-H), 5.52 (H, $\underline{NH}$), 5.61 (2H, $\underline{NH_2}$). |

## Synthesis of Sulfonyl Dipeptide Methyl Esters (16–18, 26–28) General Procedure

To a solution of amino acid methyl ester hydrochloride (0.016 mol) in THF (100 ml) was added triethylamine (5 ml), the solution was stirred at 20°C for 30 min., and cooled to 0°C, where the sulfonylamino acid (**2, 6, 7**) and (**20, 21, 23**) (0.008 mol) in THF (50 ml), and dicyclohexylcarbodiimide **DCC** (1.62 g) were added to the above mixture. The reaction mixture was stirred for 2 h at 0°C and for another 2 h at room temperature. The precipitated dicyclohexylurea was filtered off, acetic acid (1 ml) was added to the solution and left standing overnight. The precipitated was filtered off and the remaining solution was distilled under vacuum. The remaining solid was recrystallized from (ethanol-water). The products (**16–18**), (**26–28**) were to be chromatographically homogeneous.

| | |
|---|---|
| **IR** of **16, 26** | :$\nu$3300, 3100 $cm^{-1}$ (NH, CONH), 1750 $cm^{-1}$ (C=O), 1320 $cm^{-1}$ ($COOCH_3$). |
| $^1$H-**NMR** of **16, 26** | :(DMSO-$d_6$): $\delta$ 3.7 (3H, $OCH_3$), 3.8 (2H, $ArCH_2$), 9.4(1H, CONH), and other bands supporting the structure of dipeptide. |



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