Indian Journal of Chemistry
Vol. 37B, October 1998, pp. 1059 - 1062

Note

A facile synthesis and some new reactions of *N*-benzylcarboxamides with essential amino acids

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Received 6 May 1997; accepted (revised) 1 June 1998

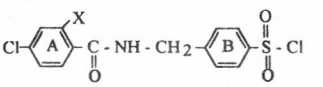
N-Benzyl-*p*-chloro and *N*-benzyl-2, 4-dichlorobenzamide react with chlorosulfonic acid to give the corresponding *p*-sulfonyl chlorides **1, 19**, which on condensation with nucleophiles give amino acid derivatives **2-7** and **20-25**. Some of the corresponding methyl esters **8-11** are also prepared. Hydrazinolysis of these methyl esters yield 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**. The spectral data are briefly discussed.

This paper is a continuation of our programme to study 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. We have reported that such compounds have biological activities[1-4].

We have demonstrated that 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 off amidic nitrogen atom.

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

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.



I, X = H 19, X = Cl

Results and Discussion

The NMR spectrum of **3** showed the resonance of the 4-protons of the phenyl ring (A) (δ 7.7) at lower field than the multiplet due to the 4-protons of ring (B) (δ 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 (δ 4.6) which was in excellent agreement with the calculated value (δ 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 $PhCH_2$, NH, and CO moieties.

N-Benzyl-*p*-chlorobenzamide reacts with chlorosulfonic acid (6 equivalent) in boiling chloroform (3 hr) to afford an excellent yield (84%) of the *p*-sulfonylchloride **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 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 sulfonyl chlorides **1, 19** showed the normal stretching absorption associated with the C=O, NH, and ArC=C groups and additionally two bands at 1380-1330 and 1180-1130 indicative of the SO_2 group[7].

All the compounds synthesized **2-28** gave IR, NMR, mass spectral data consistent with the assigned structures.

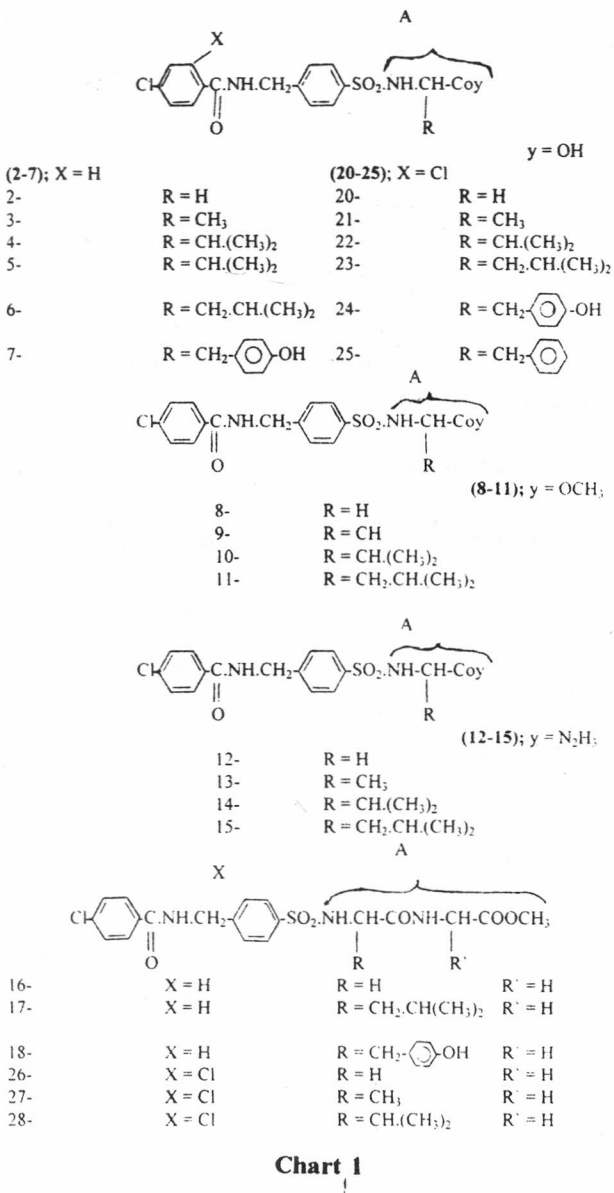


Chart 1

Experimental Section

Melting points were taken on Griffin melting point apparatus and are uncorrected. IR spectra of solid samples were run as KBr disc on a Schimadzu model 440 spectrophotometer. ^{1}H-NMR spectra were taken in DMSO-d_6 as solvent unless otherwise stated using Fx 90Q Fourier Transform. 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 to prepare 2-7, 20-25: General procedure. To an amino acid (0.1 mole) in water (25 mL) and THF (15 mL) was added triethylamine (5 mL), followed by portionwise addition of the sulfonyl chlorides (0.11 mole) during 30 min. The temperature of the reaction mixture during the process of addition was kept at 10°C. Stirring continued for 2 hr at 20°C. THF was removed by concentration of the reaction mixture under reduced pressure, water (30 mL) was added and acidified with 2 *M* HCl to *p*H 5.The crude products were filtered and recrystallized. All the products **2-7** and **20-25** were chromatographically homogenous as observed by iodine and benzidine development (cf. Table I).

IR: **3**: 3350 (NH), 1660 (C=O), 1600, 1580 (Ar C=C), 1360, 1130 (SO_2) and 760 cm^{-1} (C-Cl); **21:** 3270 (NH), 1640 (CO), 1590 (ArC=C), 1350 and 1150 cm^{-1} (SO_2).

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

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

^{1}H-NMR (DMSO-d_6) of **32**: δ 0.9 (6H, $(CH_3)_2$), 4.6 (2H, CH_2), (7.5-8.4) 7H Ar-H), 9.8 (1H, COOH); MS: m/z 473 (M^+).

Synthesis of sulfonylamino acid methyl esters 8-11: General procedure. A suspension of coupling reaction products **2, 3, 4, 6** (0.01 mole) in abs. Methanol (150 mL) was cooled to −10°C and pure thionyl chloride (1.2 mL) was added dropwise during 1 hr. The reaction mixture was stirred for an additional 3-4 hr at room temperature kept overnight and then the solvent was removed *in vacuo*. The residual solid material was recrystallised from methanol-water (cf. Table I, Chart 1).

IR: **8:** 1760, 1720 (C=O) and 1730 cm^{-1} ($COOCH_3$); ^{1}H-NMR (DMSO-d_6) of **9**: δ 7.6-8.4, (Ar-H), 3.3 (3H, OCH_3) and disappearance of OH protons.

Synthesis of sulfonylamino acid hydrazides

Table I—Physical data for the *N*-(4-sulfonylbenzyl)-4-chloro- and 2,4-dichlorobenzamides **2-18** and **20-28**

Compd	A	m.p. (°C)	Yield (%)	R_f	Mol. formula	Elemental analysis Calc. (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	$C_{23}H_{21}ClN_2O_6S$	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	$C_{19}H_{23}ClN_4O_4S$	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	133-35	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	0.61	$C_{28}H_{28}ClN_3O_6S$	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)
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	$C_{19}H_{19}Cl_2N_2O_6S$	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
						(47.79	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**.

12-15: General procedure. The methyl esters **8-11** (0.01 mol) were dissolved in ethanol (50 mL) and hydrazine hydrate 85% (0.02 mole) was added. The reaction mixture was stirred for 3 hr at 20°C and left for 24 hr 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 chromatographically homogeneous (cf. Table 1, Chart 1).

IR: **12:** 3340, 3125 (NH), 1640 (C=O), 1600, 1550 (ArC=C), 1340, 1180 (SO_2) and 690 cm^{-1} (C-Cl).

^{1}H-NMR (DMSO-d_6) of **14**: δ 9 (1H, SO_2NH), 8.1 (1H, $NH.CH_2$), 8.2-7.5 (Ar-H), 5.52 (H, NH), 5.61 (2H, 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. To this mixture were added sulfonylamino acids **2, 6, 7** and **20, 21, 23** (0.008 mole) in THF (50 mL) and dicyclohexylcarbodiimide DCC (1.62 g). The reaction mixture was stirred for 2 hr at 0°C and for another 2 hr at room temperature. The precipitated dicyclohexylurea was filtered off, acetic acid (1 mL) was added to the solution and left at standing overnight. The precipitated solid was filtered off and the remaining solution was distilled *in vacuo*. The remaining solid was recrystallized ffrom ethanol-water. The products **16-18, 26-28** were found to be chromatographically homogeneous.

IR: **16, 26:** 3300, 3100 (NH, CONH), 1750 (C=O and 1320 cm^{-1} ($COOCH_3$).

^{1}H-NMR (DMSO-d_6) of **16, 26**: δ 3.7 (3H, OCH_3), 3.8 (2H, $ArCH_2$), 9.4 (1H, CONH) and other bands supporting the structure of dipeptide; MS: m/z 488 (M^+).

References

1 El-Sayed R A, *J Serb Chem Soc,* 56, **1991,** 311

2 El-Sayed R A, Khalaf N S, Kora F A, Abbas Y A, *Pak J scient ind Res,* 34, **1991,** 369.

3 El-Sayed R A, Khalaf N S, Kora F A, Badie M F, *J Chem Soc Pak,* 14, **1992**, 49.

4 El-Sayed R A, Khalaf N S, Kora F A, El-Hakim M H, *Proc Indian nat Sci Acad,* **58,** 1992, 389-396.

5 El-Sayed R A, *J Indian chem Soc,* 96, **1992,** 618.

6 El-Sayed R A, Khalaf N S, Kora F A, El-Gazzar M A, *J Serb Chem Soc,* 59, **1994,** 727.

7 Bellamy L J, *Infra-red spectra of complex molecules,* 2nd Edn (Publishern addsey, London), 1966.

8 Cremlyn R J W, Ellis L & Pinney A, *Phosphorus, Sulfur, and Silicon,* 44, **1989,** 167.