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SYNTHESIS OF SULTAMS BY CYCLOALKYLATION OF (ALKOXYCARBONYL-METHANE)SULFONANILIDES

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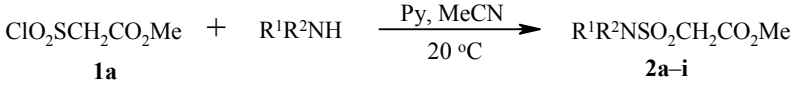
(Methoxycarbonylmethane)sulfonanilides are alkylated by α,ω-dihaloalkanes in K_2CO_3–DMF with the formation of sultams. A high sensitivity has been detected for the reaction rate on the electronic effect of substituents in the aromatic nucleus, although substituents in the ortho position do not obstruct the reaction and in the case of 2,6-disubstituted derivatives the reaction rate and sultam yield were maximal. Tertiary sulfonamides form derivatives of 1-sulfamoylcyclopropanecarboxylic acid under these conditions.

Keywords: (methoxycarbonylmethane)sulfonanilides, sultams, cyclopropanes, heterocyclization.

Many compounds having a sulfonamide group in their composition are used in medicinal practice, for example as antibacterial or hypoglycemic preparations [1, 2]. To this day interest in sulfonamides as potential medicinal preparations is fairly great [3. 4].

Although the generally applied method of obtaining sulfonamides is the interaction of sulfonyl chlorides with amines, the synthesis of cyclic analogues (sultams) is not so simple. One of the possible solutions is the intramolecular alkylation of sulfonamides where means of creating an electrophilic center may be varied. In this connection cycloalkylation with the participation of sulfonamides having an additional C-nucleophilic center with dihalides or their equivalent may possess obvious merit.

From this point of view the sulfonamides **2** obtained from readily available alkoxycarbonyl-methanesulfonyl chlorides **1a,b** may posses a high potential [5]. Although heterocyclization of these sulfonamides by intramolecular condensation of carbonyl and active methylene groups [6] or transposition of C,N-diallyl derivatives [7] is known, their alkylation by aliphatic dihalides has not been described and attracted our attention.



2 a R^1 = Ph, **b** R^1 = Ph, **c** R^1 = 2-MeC_6H_4, **d** R^1 = 4-MeC_6H_4, **e** R^1 = 2,6-$Me_2C_6H_3$, **f** R^1 = 4-ClC_6H_4, **g** R^1 = 3,5-$Cl_2C_6H_3$, **h** R^1 = 4-MeC_6H_4, **i** R^1 = 4-$EtOCOC_6H_4$; **a**, **c**–**i** R^2 = H, **b** R^2 = Me

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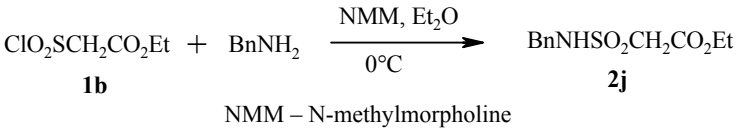
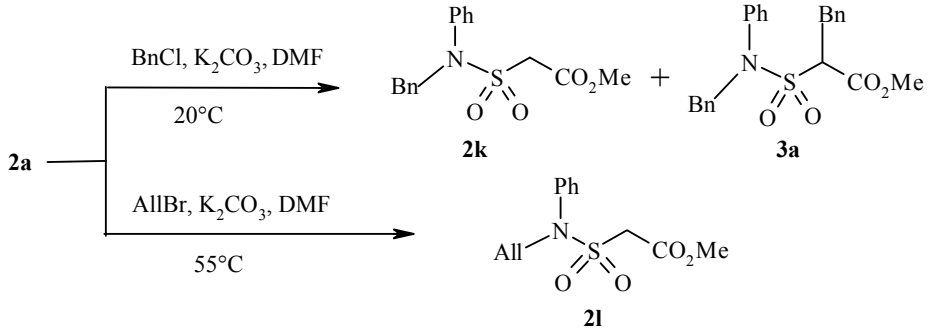
Sulfonamides **2a-i** were obtained as starting materials (Tables 1, 2).

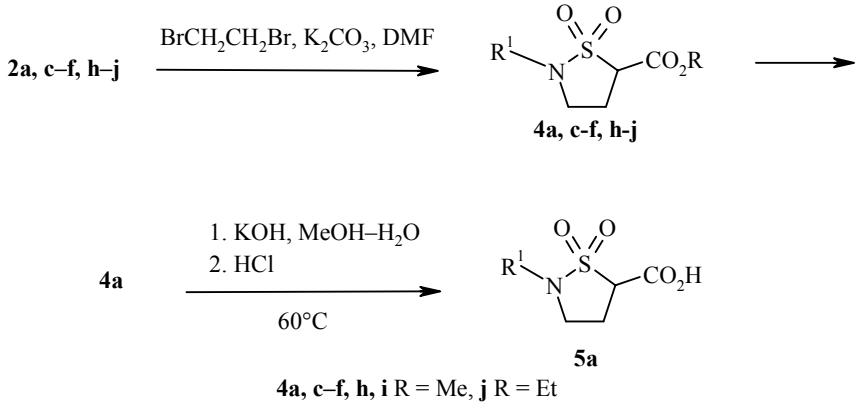
The interaction of sulfonyl chloride **1a** with anilines took place without complications from the ester group and led to sulfonamides **2a-i** in high yield. However in the aliphatic series even the not very nucleophilic benzylamine begins to react competitively with the ester. In order to avoid this complication in obtaining N-benzylamide **2j** it was necessary to use ethyl ester **1b** and carry out the reaction at reduced temperature.



Two nucleophilic centers exist in sulfonamides **2a,c-j** with no clear previous relative reactivity. In reality on interacting sulfonamide **2a** with an equivalent amount of benzyl chloride in the system K_2CO_3–DMF a mixture is formed of the products of N- and C,N-alkylation (**2k** and **3a** respectively) in a 4:3 ratio.



However on using a dilute solution of allyl bromide the reaction was carried out successfully and the sole product was that of N-alkylation **2l**.



Alkylation of sulfonamides **2a,c-j** with 1,2-dibromoethane in the same system led to the desired sultams **4** (Tables 3, 4). With a high degree of conversion of sulfonamide **2a** the formation was observed of a product of further alkylation of unestablished structure. A change to the less polar acetonitrile or a protic solvent, and also replacement of potassium carbonate by a weaker base might increase the yield of sultam **4a**. However the reaction did not proceed in methanol, and on using acetonitrile in combination with various bases (calcium carbonate, triethylamine, N,N-dimethylaniline) its rate was heavily reduced.

TABLE 1. Alkoxycarbonylmethanesulfonamides **2a-j**

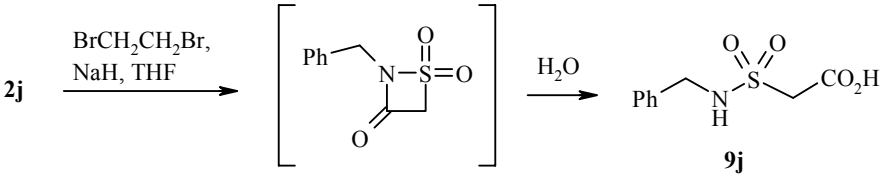
Compound	Empirical formula	Found, % / Calculated, %			mp, ºC	Yield, %
		C	H	N		
2a	$C_9H_{11}NO_4S$				79-80 [7]	74
2b	$C_{10}H_{13}NO_4S$	49.36 / 49.37	5.38 / 5.39	5.93 / 5.76	63-64	79
2c	$C_{10}H_{13}NO_4S$	49.20 / 49.37	5.50 / 5.39	6.05 / 5.76	55-56	72
2d	$C_{10}H_{13}NO_4S$	49.36 / 49.37	5.60 / 5.39	6.02 / 5.76	77-79	85
2e	$C_{11}H_{15}NO_4S$	51.42 / 51.35	5.74 / 5.88	5.57 / 5.44	105-106	82
2f	$C_9H_{10}ClNO_4S$	41.12 / 40.99	4.09 / 3.82	5.33 / 5.31	99-100	72
2g	$C_9H_9Cl_2NO_4S$	36.03 / 36.26	3.18 / 3.04	4.73 / 4.70	132-133	78
2h	$C_{10}H_{13}NO_5S$	46.23 / 46.32	5.05 / 5.05	5.54 / 5.40	85-86	71
2i	$C_{12}H_{15}NO_6S$	47.63 / 47.83	4.98 / 5.02	4.62 / 4.65	98-99	83
2j	$C_{11}H_{15}NO_4S$	51.42 / 51.35	5.67 / 5.88	5.30 / 5.44	56-57	60

The K_2CO_3–DMF system therefore proved to be the most suitable for obtaining sultam **4a** in dilute solution.

To clarify the limits of applicability of the reaction, the set of sulfonamides **2a,c-i** and several α,ω-dihaloalkanes were studied. As a result it became clear that in the case of sulfonanilides the given reaction is extremely sensitive to the electronic effect of substituents. Electron-withdrawing groups strongly slowed the process, and for its completion extended stirring at a higher temperature is necessary than in the case of sulfonamide **2a**. It is evident that this is linked with the reduced nucleophilicity of the resulting anion. Donor substituents in the benzene ring, on the other hand, aid the passage of the reaction. Sulfonanilides **2d,h** reacted more rapidly than sulfonanilide **2a**.

In addition it was discovered that substituents in the *ortho* position do not prevent this reaction, and in the case of sulfonamide **2e** the reaction proceeds most rapidly and with maximal yield. A possible explanation is that in the present case, due to the loss of a portion of the degree of freedom, the loss in entropy of the system as a result of the reaction is less than in the case of other sulfonamides, which is analogous to the well known *gem*-dialkyl effect in cyclization reactions [9]. The high steric strain of the products of cycloalkylation of sulfonamide **2e** with all three α,ω-dihaloalkanes is confirmed, judging by the diastereotopicity of the C-methyl groups according to NMR spectra.

On reacting N-benzylsulfonamide **2j** with dibromoethane a multicomponent mixture is formed, the resolution of which made it possible to obtain ethyl 2-benzyl-1,2-thiazolidine-5-carboxylate 1,1-dioxide (**4j**) in extremely small yield. Such a result is probably linked with the low acidity of sulfonamide **2j**, consequently the use of a stronger base might have aided the reaction process. However in the system NaH–THF (benzylaminosulfonyl)acetic acid (**9j**) was obtained in quantitative yield. In passing, this reaction goes through the intermediate formation of a β-lactam.



9j

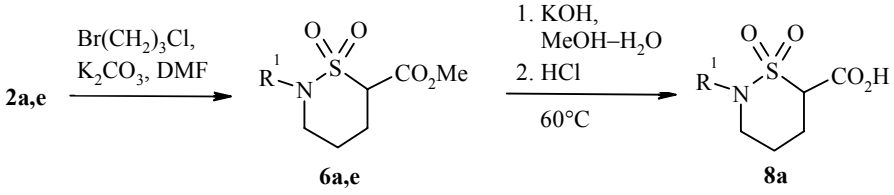
TABLE 2. Spectral Characteristics of Sulfonamides **2b-j**

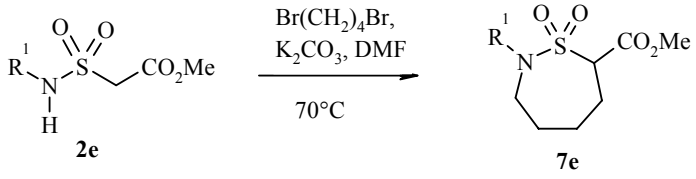
Com-pound	^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz)	^{13}C NMR spectrum ($CDCl_3$), δ, ppm	Mass-spectrum, *m/z* (I_{rel}, %)
2b	3.43 (3H, s, NCH_3); 3.82 (3H, s, OCH_3); 3.98 (2H, s, SO_2CH_2), 7.32-7.51 (5H, m, ArH)	39.9 (NCH_3), 53.3 (OCH_3), 53.9 (SO_2CH_2), 127.2 (*o*/*m*-C_{Ar}), 128.1 (*p*-C_{Ar}), 129.6 (*m*/*o*-C_{Ar}), 140.7 (*ipso*-C_{Ar}), 164.0 (CO)	243 $[M]^+$ (71), 106 (100), 104 (15), 79 (21), 77 (38), 42 (15)
2c	2.41 (3H, s, CCH_3); 3.82 (3H, s, OCH_3); 4.08 (2H, s, SO_2CH_2); 6.79 (1H, s, NH); 7.15-7.28 (3H, m, ArH); 7.51 (1H, d, *J* = 7.3, ArH)	18.0 ($C\underline{C}H_3$), 53.3 (OCH_3), 54.1 (SO_2CH_2), 123.0 ($C_{Ar}H$), 126.7 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 131.5 ($C_{Ar}H$), 132.2 (C_{Ar}), 134.4 (C_{Ar}), 164.3 (CO)	243 $[M]^+$ (12), 106 (100), 79 (10), 77 (19)
2d	2.35 (3H, s, CCH_3); 3.84 (3H, s, OCH_3); 3.95 (2H, s, SO_2CH_2); 6.91 (1H, s, NH); 7.17-7.25 (4H, m, ArH)	21.0 ($C\underline{C}H_3$), 52.7 (SO_2CH_2), 53.4 (OCH_3), 123.1 (2,6-C_{Ar}), 130.3 (3,5-C_{Ar}), 133.4 (1/4-C_{Ar}), 136.6 (4/1-C_{Ar}), 164.6 (CO)	243 $[M]^+$ (27), 211 (12), 106 (100), 79 (28), 77 (32)
2e	2.42 (6H, s, $2CH_3$); 3.85 (3H, s, OCH_3); 4.20 (2H, s, SO_2CH_2); 6.68 (1H, s, NH); 7.08-7.17 (3H, m, ArH)	19.2 ($C\underline{C}H_3$), 53.3 (OCH_3), 57.7 (SO_2CH_2), 128.2 (4-C_{Ar}), 128.9 (3,5-C_{Ar}), 132.5 (1-C_{Ar}), 137.7 (2,6-C_{Ar}), 164.8 (CO)	257 $[M]^+$ (8), 120 (100), 91 (12)
2f	3.82 (3H, s, OCH_3); 3.98 (2H, s, SO_2CH_2); 7.26 (1H, s, NH); 7.27-7.36 (4H, m, ArH)	53.0 (SO_2CH_2), 53.5 (OCH_3), 124.0 (2,6-C_{Ar}), 129.9 (3,5-C_{Ar}), 132.2 (1/4-C_{Ar}), 134.7 (4/1-C_{Ar}), 164.4 (CO)	263 $[M]^+$ (21), 231 (28), 126 (100), 99 (50)
2g	3.85 (3H, s, OCH_3); 4.03 (2H, s, SO_2CH_2); 7.24-7.27 (4H, m, ArH)	53.6 (SO_2CH_2), 53.7 (OCH_3), 120.2 (2,6-C_{Ar}), 126.4 (4-C_{Ar}), 136.1 (3,5-C_{Ar}), 138.2 (1-C_{Ar}), 164.3 (CO)	297 $[M]^+$ (100), 265 (92), 223 (22), 187 (58), 160 (50), 133 (78), 104 (32), 90 (20), 63 (36), 45 (23)
2h	3.82 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 3.93 (2H, s, SO_2CH_2); 6.87 (1H, s, NH); 6.91 (2H, d, *J* = 8.7, 3,5-ArH); 7.30 (2H, d, *J* = 8.7, 2,6-ArH)	52.6 (SO_2CH_2), 53.4 (OCH_3), 55.6 (OCH_3), 114.9 (3,5-C_{Ar}), 125.6 (2,6-C_{Ar}), 128.6 (1-C_{Ar}), 158.6 (4-C_{Ar}), 164.6 (CO)	259 $[M]^+$ (10), 122 (100), 95 (16)
2i	1.40 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 3.81 (3H, s, OCH_3); 4.0 (2H, s, SO_2CH_2); 4.38 (2H, q, *J* = 7, $C\underline{H}_2CH_3$); 7.37 (2H, d, *J* = 8.7, 2,6-ArH); 7.47 (1H, s, NH); 8.06 (2H, d, *J* = 8.7, 3,5-ArH)	14.4 ($CH_2\underline{C}H_3$), 53.5 (OCH_3), 53.62 (SO_2CH_2), 61.3 (OCH_2), 120.5 (2,6-C_{Ar}), 127.9 (4-C_{Ar}), 131.4 (3,5-C_{Ar}), 140.5 (1-C_{Ar}), 164.1 (CO), 165.9 (CO)	301 $[M]^+$ (100), 256 (48), 241 (48), 182 (57), 163 (90), 119 (38), 108 (95), 91 (50), 64 (33), 42 (17)
2j	1.30 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 3.89 (2H, s, SO_2CH_2); 4.23 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 4.36 (2H, d, *J* = 6.5, NCH_2); 5.30 (1H, t, *J* = 6.5, NH); 7.30-7.41 (5H, m, ArH)	14.1 ($CH_2\underline{C}H_3$), 47.9 (NCH_2), 55.7 (SO_2CH_2), 62.6 (OCH_2), 128.3 (*o*/*m*-C_{Ar}), 128.3 (*p*-C_{Ar}), 129.0 (*m*/*o*-C_{Ar}), 136.2 (*ipso*-C_{Ar}), 164.2 (CO)	106 (100), 91 (40), 88 (10), 77 (22), 60 (16), 51 (15), 42 (17)

TABLE 3. Sultams

Compound	Empirical formula	Found, % / Calculated, %			mp, ºC	Yield, %
		C	H	N		
4a	$C_{11}H_{13}NO_4S$	51.69 / 51.75	5.15 / 5.13	5.56 / 5.56	96-97	70
4c	$C_{12}H_{15}NO_4S$	53.40 / 53.52	5.62 / 5.61	5.07 / 5.20	69-70	68
4d	$C_{12}H_{15}NO_4S$	53.43 / 53.52	5.54 / 5.61	5.18 / 5.20	99-100	76
4e	$C_{13}H_{17}NO_4S$	55.19 / 55.12	6.11 / 6.05	4.89 / 4.94	107-108	86
4f	$C_{11}H_{12}ClNO_4S$	45.48 / 45.60	4.12 / 4.17	4.89 / 4.83	121-122	56
4h	$C_{12}H_{15}NO_5S$	50.58 / 50.53	5.26 / 5.26	4.93 / 4.91	125-126	74
4i	$C_{14}H_{17}NO_6S$	51.48 / 51.37	5.31 / 5.23	4.12 / 4.28	143-144	18
4j	$C_{13}H_{17}NO_4S$				—	1.5
6a	$C_{12}H_{15}NO_4S$	53.40 / 53.52	5.60 / 5.61	5.20 / 5.20	59-60	73
6e	$C_{14}H_{19}NO_4S$	56.46 / 56.55	6.44 / 6.44	4.72 / 4.71	172-174	84
7e	$C_{15}H_{21}NO_4S$	57.86 / 57.86	6.91 / 6.80	4.45 / 4.50	127-128	27
10a	$C_{17}H_{17}NO_4S$	61.48 / 61.61	5.31 / 5.17	4.27 / 4.23	137-138	53

To clarify the possibility of obtaining six- and seven-membered derivatives the alkylation of sulfonamides **2a,e** with 1-bromo-3-chloropropane and 1,4-dibromobutane was investigated.

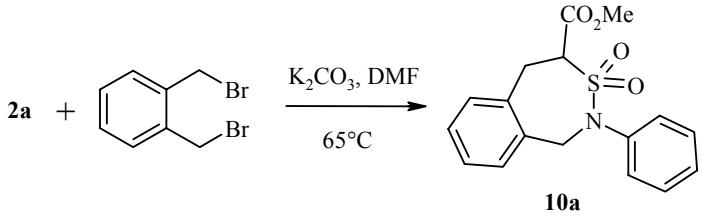




1-Bromo-3-chloropropane reacts somewhat more slowly than dibromoethane. In the present case slower addition of alkylating agent is required otherwise several products are formed. As expected, sulfonamide **2e**, which was the most reactive in the reaction with dibromoethane, reacted far more rapidly in the present case than the unsubstituted analog **2a**.

More vigorous and extended heating was required to carry out the reaction with 1,4-dibromobutane. In the case of sulfonamide **2e** we successfully isolated methyl 2-(2,6-dimethylphenyl)-1,2-thiazepane-7-carboxylate 1,1-dioxide (**7e**) in 27% yield, but in the case of amide **2a** a multicomponent mixture was formed, resolution of which was unsuccessful. This result is fairly logical since the rate of formation of seven-

membered rings is far lower than that of five- and six-membered. However on using a sterically more rigid alkylating agent the probability of intramolecular reaction grows. Thus on alkylating sulfonamide **2a** with 1,2-bis(bromomethyl)benzene 4-methoxycarbonyl-2-phenyl-1,2,4,5-tetrahydro[*d*][1,2]thiazepine 3,3-dioxide (**10a**) was successfully isolated in 53% yield.

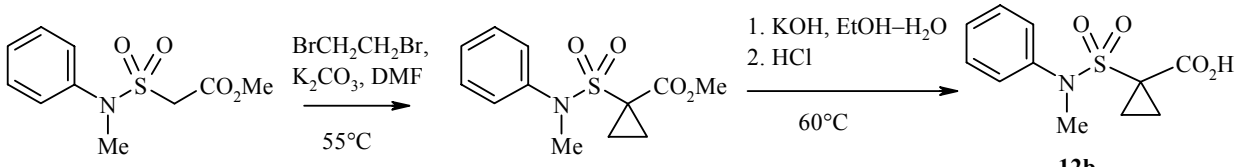


10a

In the ^{1}H NMR (but not the ^{13}C) spectrum of this compound a strong broadening was observed of the proton signals of the seven-membered ring, which indicates the presence of a conformational coalescence transition close to room temperature.

All the obtained sultams **4-7** contain an ester grouping which may be hydrolyzed under mild conditions with the formation of the corresponding acids **5a, 8a** without decarboxylation, which opens the possibility of further functionalization at the carboxyl group.

For the tertiary sulfonamide **2b** it was shown possible to obtain the cyclopropane derivative **11b** in high yield.



2b **11b** **12b**

The obtained ester **11b** was readily hydrolyzed to the corresponding acid **12b**, and on boiling the latter for 15 h in N,N-dimethylacetamide no decarboxylation occurred.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were taken on a Bruker DPX 300 instrument (300 and 75 MHz respectively) in $CDCl_3$. Chemical shifts were determined relative to the solvent signal in ^{1}H NMR spectra: 7.26 (for $CHCl_3$) and 2.49 ppm (for DMSO-d_5); in ^{13}C NMR spectra: 77.1 (for $CDCl_3$), 39.5 (for DMSO-d_6) and 204.1 ppm (acetone-d_6). Coupling constants in proton spectra were measured to a first order approximation. The standard impulse sequence DEPT-135 was used to determine the multiplicity of signals in the ^{13}C NMR spectra. Mass spectra were obtained on a Finnigan MAT Incos 50 instrument, ionization by electron impact (EI) with energy of ionizing electrons 70 eV. Elemental analyses were carried out on a Hewlett Packard HP-185B automatic CHN analyzer. The degree of progress of a reaction, the R_f values, and purity of products was checked by TLC on ALUGRAM® SIL G/UV_{254}, eluent ethyl acetate–hexane, 1:2, if not shown otherwise.

TABLE 4. ^{1}H and ^{13}C NMR Spectra and Mass Spectra of Sultams

Compound	^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz)	^{13}C NMR spectrum ($CDCl_3$), δ, ppm	Mass spectrum, *m/z* (I_{rel}, %)
1	2	3	4
4a	2.67 (1H, m, H-4); 2.90 (1H, m, H-4'); 3.76 (1H, dt, *J* = 6.9 and *J* = 8.7, H-3); 3.91 (3H, s, OCH_3); 3.93 (1H, m, H-3'); 4.30 (1H, dd, *J* = 6.9 and *J* = 8.7, H-5); 7.20-7.42 (5H, m, ArH)	22.1 (C-4), 45.4 (C-3), 53.8 (OCH_3), 62.0 (C-5), 121.2 (*o*-C_{Ar}), 125.7 (*p*-C_{Ar}), 129.5 (*m*-C_{Ar}), 137.2 (*ipso*-C_{Ar}), 165.0 (CO)	255 $[M]^+$ (38), 160 (12), 132 (100), 104 (83), 77 (81), 51 (29), 39 (18)
4c	2.39 (3H, s, CCH_3); 2.68 (1H, m, H-4); 2.89 (1H, m, H-4'); 3.65 (1H, dt, *J* = 5.5 and *J* = 8.7, H-3); 3.79 (1H, dt, *J* = 5.8 and *J* = 8.7, H-3'); 3.91 (3H, s, OCH_3); 4.26 (1H, dd, *J* = 5.5 and *J* = 8.4, H-5); 7.24-7.43 (4H, m, ArH)	18.0 ($C\underline{C}H_3$), 22.6 (C-4), 47.6 (C-3), 53.7 (OCH_3), 60.8 (C-5), 127.2 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 129.0 ($C_{Ar}H$), 131.5 ($C_{Ar}H$), 134.7 (C_{Ar}), 139.1 (C_{Ar}), 165.8 (CO)	269 $[M]^+$ (12), 146 (51), 118 (100), 91 (35), 65 (22), 55 (18), 39 (17)
4d	2.35 (3H, s, CCH_3); 2.64 (1H, m, H-4); 2.88 (1H, m, H-4'); 3.73 (1H, dt, *J* = 6.9 and *J* = 8.7, H-3); 3.86 (1H, m, H-3'); 3.96 (3H, s, OCH_3); 4.26 (1H, dd, *J* = 5.5 and 8.4, H-5); 7.17-7.23 (4H, m, ArH)	21.0 ($C\underline{C}H_3$), 22.2 (C-4), 45.8 (C-3), 53.8 (OCH_3), 61.8 (C-5), 122.3 (C_{Ar}-2,6), 130.2 (C_{Ar}-3,5), 134.4 (C_{Ar}-1/4), 136.1 (C_{Ar}-4/1), 165.2 (CO)	269 $[M]^+$ (32), 146 (60), 130 (10), 119 (100), 91 (82), 77 (12), 65 (40), 55 (32), 39 (29)
4e	2.38 (3H, s, CCH_3); 2.41 (3H, s, CCH_3); 2.73 (1H, m, H-4); 2.93 (1H, m, H-4'); 3.60 (1H, dt, *J* = 5.8 and *J* = 8.7, H-3); 3.90 (1H, dt, *J* = 5.8 and *J* = 8.7, H-3'); 3.90 (3H, s, OCH_3); 4,22 (1H, t, *J* = 7.62, H-5); 7.09-7.20 (3H, m, ArH)	18.4 ($C\underline{C}H_3$), 18.6 ($C\underline{C}H_3$), 22.5 (C-4), 45.3 (C-3), 53.5 (OCH_3), 60.6 (C-5), 129.1 (C_{Ar}-3,5), 129.2 (C_{Ar}-4), 132.3 (C_{Ar}-1), 139.8 (C_{Ar}-2/6), 140.6 (C_{Ar}-6/2), 165.3 (CO)	283 $[M]^+$ (12), 204 (22), 160 (31), 132 (100), 117 (30), 105 (20), 91 (12), 77 (21), 55 (22), 39 (18).
4f	2.67 (1H, m, H-4); 2.82 (1H, m, H-4'); 3.72 (1H, m, H-3); 3.91 (3H, s, OCH_3); 3.82 (1H, m, H-3'); 4.29 (1H, t, *J* = 7.3, H-5); 7.23-7.37 (4H, m, ArH)	22.1 (C-4), 45.5 (C-3), 53.9 (OCH_3), 61.9 (C-5), 122.7 (C_{Ar}-2,6), 129.7 (C_{Ar}-3,5), 131.4 (C_{Ar}-1/4), 135.8 (C_{Ar}-4/1), 164.9 (CO)	289 $[M]^+$ (15), 166 (62), 139 (100), 111 (62), 75 (40), 55 (40), 39 (20)
4h	2.63 (1H, m, H-4); 2.73 (1H, m, H-4'); 3.69 (1H, m, H-3); 3.81 (3H, s, OCH_3); 3.82 (1H, m, H-3'); 3.90 (3H, s, OCH_3); 4.27 (1H, dd, *J* = 6.5 and *J* = 8.7, H-5); 6.89-6.95 (2H, m, 3,5-ArH); 7.25-7.30 (2H, m, 2,6-ArH)	22.3 (C-4), 46.6 (C-3), 53.7 (OCH_3), 55.6 (OCH_3), 61.4 (C-5), 114.9 (C_{Ar}-3,5), 125.8 (C_{Ar}-2,6), 129.4 (C_{Ar}-1), 158.6 (C_{Ar}-4), 165.4 (CO)	285 $[M]^+$ (18), 162 (25), 135 (100), 120 (63), 92 (23), 65 (15), 55 (24), 39 (28)

TABLE 4. (continued)

1	2	3	4
4i	1.39 (3H, t, J = 6.9, $OCH_2C\underline{H}_3$); 2.70 (1H, m, H-4); 2.86 (1H, m, J = 6.5 and J = 7.3, H-4'); 3.78 (1H, m, H-3); 3.89 (3H, s, OCH_3); 3.97 (1H, m, H-3'); 4.28–4.39 (3H, m); 7.27 (1H, d, J = 8.0, 2,6-ArH); 8.04 (1H, d, J = 8.0, 3,5-ArH)	14.5 ($CH_2\underline{C}H_3$), 22.0 (C-4), 44.9 (C-3), 53.9 (OCH_3), 61.1 (OCH_2), 62.4 (C-5), 118.1 (C_{Ar}-2,6), 126.4 (C_{Ar}-4), 131.1 (C_{Ar}-3,5), 141.6 (C_{Ar}-1), 164.6 (CO), 166.1 (CO)	327 $[M]^+$ (18), 218 (14), 204 (54), 174 (55), 149 (18), 132 (100), 104 (26), 77 (52), 64 (20), 55 (32)
4j	1.36 (3H, t, J = 6.9, $OCH_2C\underline{H}_3$); 2.43 (1H, m, H-4); 2.67 (1H, m, H-4'); 3.10 (1H, ddd, J = 5.8, J = 8.0 and J = 9.5, H-3); 3.23 (1H, ddd, J = 5.8, J = 8.0 and J = 9.5, H-3'); 4.11 (1H, dd, J = 5.8 and J = 8.7, H-5); 4.18 (1H, d, J = 14.5, $C_{Ar}C\underline{H}H'$); 4.26 (1H, d, J = 14.5, $C_{Ar}CH\underline{H}'$); 4.27-4.42 (2H, m); 7.30-7.33 (5H, m, ArH)	14.0 ($CH_2\underline{C}H_3$), 22.2 (C-4), 44.2 (CH_2), 49.1 (CH_2), 60.9 (C-5), 62.6 (OCH_2), 128.0 (*p*-C_{Ar}), 128.4 (*o/m*-C_{Ar}), 128.7 (*m/o*-C_{Ar}), 135.3 (*ipso*-C_{Ar}), 165.0 (CO)	262 $[M–1]^+$ (11), 206 (24), 146 (15), 119 (12), 91 (100)
6a	1.95 (1H, m); 2.10 (1H, m); 2.59 (2H, m); 3.74 (1H, dt, J = 4.5 and J = 13.8, H-3); 3.82 (3H, s, OCH_3); 3.95-4.01 (1H, m); 4.08 (1H, dd, J = 4.4 and J = 9.6, H-6); 7.27-7.40 (5H, m, ArH)	23.0 (CH_2), 28.0 (CH_2), 53.3 (C-3), 53.3 (OCH_3), 63.7 (C-6), 126.8 (*o/m*-C_{Ar}), 127.4 (*p*-C_{Ar}), 129.2 (*m/o*-C_{Ar}), 140.7 (*ipso*-C_{Ar}), 165.7 (CO)	269 $[M]^+$ (50), 146 (52), 119 (100), 105 (90), 91 (30), 77 (86), 64 (18), 55 (28), 51 (49), 39 (42)
6e	1.96-2.03 (2H, m); 2.41 (3H, s, CCH_3); 2.42 (3H, s, CCH_3); 2.50-2.72 (2H, m); 3.33 (1H, d, J = 13.1, H-3); 3.85 (3H, s, OCH_3); 4.04 (1H, m, H-3'); 4.16 (1H, dd, J = 4.0 and J = 11.4, H-6); 7.06-7.14 (3H, m, ArH)	19.4 ($C\underline{C}H_3$), 20.1 ($C\underline{C}H_3$), 24.7 (CH_2), 28.3 (CH_2), 52.2 (C-3), 53.3 (OCH_3) 65.0 (C-6), 128.4 (C_{Ar}-3/4/5), 128.7 (C_{Ar}-4/5/3), 129.3 (C_{Ar}-5/3/4), 138.0 (C_{Ar}-1/2/6), 138.8 (C_{Ar}-2/6/1), 138.9 (C_{Ar}-6/1/2), 165.6 (CO)	297 $[M]^+$ (7), 218 (25), 174 (100), 132 (65), 117 (19), 105 (21), 91 (11), 77 (22), 55 (16), 39 (22)
7e	1.73-1.83 (1H, m); 2.06-2.37 (5H, m); 2.41 (3H, s, CCH_3); 2.47 (3H, s, CCH_3); 2.98 (1H, dt, J = 5.8 and J = 12.1); 3.64 (1H, ddd, J = 2.8, J = 5.3 and J = 12.1); 3.80 (3H, s, OCH_3); 4.15 (1H, dd, J = 4.6 and J = 11.1, H-7); 7.07-7.15 (3H, m, ArH)	19.2 ($C\underline{C}H_3$), 19.8 ($C\underline{C}H_3$), 25.3 (CH_2), 27.7 (CH_2), 28.8 (CH_2), 50.6 (C-3), 53.2 (OCH_3), 71.7 (C-7), 128.5 (3/4/5-C_{Ar}), 129.2 (4/5/3-C_{Ar}), 129.5 (5/3/4-C_{Ar}), 136.4 (1-C_{Ar}), 139.6 (C_{Ar}-2,6), 166.8 (CO)	311 $[M]^+$ (6), 280 (11), 247 (14), 188 (39), 177 (16), 132 (100), 105 (16), 77 (16), 39 (16)
10a	3.47 (1H, d, J = 15.3, H-5); 3.78 (4H, m); 4.08 (1H, d, J = 10.9, H-4); 4.38 (1H, br. s, H-1); 5.18 (1H, br. s, H-1'); 6.80 (2H, d, J = 10.9, ArH); 7.02 (1H, d, J = 10.9, ArH); 7.20-7.40 (6H, m, ArH)	34.6 (C-5), 53.4 (OCH_3), 55.9 (C-1), 67.0 (C-4), 128.2 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 129.0 ($2C_{Ar}H$), 129.3 ($3C_{Ar}H$), 130.2 ($C_{Ar}H$), 131.4 ($C_{Ar}H$), 136.7 (C_{Ar}), 138.4 (C_{Ar}), 139.8 (C_{Ar}), 166.0 (CO)	331 $[M]^+$ (10), 206 (27), 116 (100), 104 (24), 93 (59), 77 (79), 64 (23), 59 (26), 51 (47), 39 (32)

Methoxycarbonylmethanesulfonyl chloride (1a). Yield 77%; bp 115-116°C (15 mm Hg) [10].

Ethoxycarbonylmethanesulfonyl chloride (1b). Yield 72%; bp 124-126°C (15 mm Hg) [11].

Synthesis of Methoxycarbonylmethanesulfonyl Amides 2a-i (General Method). Ester **1a** (17.25 g, 100 mmol) dissolved in acetonitrile (30 ml) was added slowly to a stirred solution of arylamine (110 mmol) and pyridine (8.96 g, 110 mmol) in acetonitrile (70 ml) at 15-20°C. The reaction mixture was heated to 35°C and maintained at the same temperature for 15 min. The mixture was diluted with water (600 ml) with stirring, and acidified with conc. HCl to pH ≤2. The precipitated solid was filtered off and recrystallized from a mixture of diethyl ether and hexane.

4'-Methoxy(methoxycarbonyl)methanesulfonanilide (2h) was synthesized previously [3], but not characterized.

N-Benzyl(ethoxycarbonyl)methanesulfonamide (2j). A mixture of benzylamine (5.35 g, 50 mmol) and N-methylmorpholine (5.05 g, 50 mmol) in ether (50 ml) was added dropwise with stirring and cooling to a solution of sulfonyl chloride **1b** (9.3 g, 50 mmol) in diethyl ether (100 ml) at such a rate that the temperature did not exceed 2°C. The reaction mixture was then diluted with water (150 ml) and acidified with conc. HCl to pH ≤2. The ether layer was separated, and the aqueous layer extracted with dichloromethane (2×30 ml). The organic phases were combined, dried over sodium sulfate, and evaporated to dryness. The product was recrystallized from diethyl ether. Yield was 60%; mp 56-57°C.

N-Benzyl(methoxycarbonyl)methanesulfonanilide (2k). Benzyl chloride (0.5 g, 4 mmol) was added to a mixture of sulfonamide **2a** (0.92 g, 4 mmol) and potassium carbonate (0.83 g, 6 mmol) in DMF (40 ml). The reaction mixture was stirred for 1 h at 20°C, after which it was heated to 40°C and stirred for 1 h further, then diluted with water (100 ml), acidified to pH ≤2, and extracted with dichloromethane (3×50 ml). The organic layer was washed with 2% HCl (5×80 ml), dried over sodium sulphate, and evaporated to dryness. The product was isolated by chromatography on silica gel (eluent ethyl acetate–hexane, 1:2, R_f 0.4). Yield was 24%, light-yellow oil. ^{1}H NMR spectrum, δ, ppm: 3.88 (3H, s, OCH_3); 4.05 (2H, s, SO_2CH_2); 4.94 (2H, s, NCH_2); 7.22-7.41 (10H, m, ArH). ^{13}C NMR spectrum, δ, ppm: 53.2 (OCH_3); 54.5 (CH_2); 57.0 (CH_2); 127.9 ($C_{Ar}H$), 128.5 ($C_{Ar}H$); 128.5 ($C_{Ar}H$); 128.6 ($C_{Ar}H$); 129.5 ($C_{Ar}H$); 129.5 ($C_{Ar}H$); 136.3 (C_{Ar}); 138.3 (C_{Ar}); 164.2 (CO). Mass spectrum, *m/z* (I_{rel}, %): 319 (8) $[M]^+$, 181 (18), 104 (12), 91 (100), 84 (30), 77 (25), 51 (11). An analytically pure sample was not successfully obtained.

N-Allyl(methoxycarbonyl)methanesulfonanilide (2l). Allyl bromide (0.48 g, 4 mmol) was added with stirring at 55°C during 1.5 h to a mixture of sulfonamide **2a** (0.92 g, 4 mmol) and potassium carbonate (0.83 g, 6 mmol) in DMF (60 ml). The product was isolated analogously to sulfonamide **2k**. Yield was 68%, brown oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.83 (3H, s, OCH_3); 3.99 (2H, s, SO_2CH_2); 4.36 (2H, d, J = 6.5, NCH_2); 5.09-5.16 (2H, m, CH=C$\underline{H}_2$); 5.80 (1H, ddt, J = 6.5, J = 10.2, and J = 16.7, C$\underline{H}$=CH_2); 7.34-7.47 (5H, m, ArH). ^{13}C NMR spectrum, δ, ppm: 53.2 (OCH_3); 54.6 (CH_2); 55.6 (CH_2); 119.0 (CH=$\underline{C}H_2$); 128.5 (*p*-C_{Ar}); 129.3 (*o/m*-C_{Ar}); 129.5 (*m/o*-C_{Ar}); 133.1 ($\underline{C}$H=CH_2); 138.4 (*ipso*-C_{Ar}); 164.0 (CO). Mass spectrum, *m/z* (I_{rel}, %): 269 $[M]^+$ (24), 238 (10), 132 (100), 117 (51), 104 (79), 91 (35), 77 (94), 65 (16), 57 (18), 51 (32). An analytically pure sample was not successfully obtained.

Methyl 2-(N-benzyl-N-phenylaminosulfonyl)-3-phenylpropionate (3a) was obtained analogously to sulfonamide **2k**, R_f 0.3. Yield was 16%; mp 115-116°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.38 (1H, dd, J = 12.8 and J = 13.7, CHC$\underline{H}$H'), 3.50 (1H, dd, J = 4.7 and J = 13.7, CHCH$\underline{H}$'); 3.75 (3H, s, OCH_3); 4.29 (1H, dd, J = 4.7 and J = 12.8, C$\underline{H}CH_2$), 4.72 (1H, d, J = 14.5, NC$\underline{H}$H'); 4.96 (1H, d, J = 14.5, NCH$\underline{H}$'); 7.16-7.27 (15H, m, ArH). ^{13}C NMR spectrum, δ, ppm: 33.8 (CH$\underline{C}H_2$); 53.1 (OCH_3); 57.1 (NCH_2); 68.5 ($\underline{C}HCH_2$); 127.4 ($C_{Ar}H$); 128.0 ($C_{Ar}H$); 128.4 ($C_{Ar}H$); 128.5 ($C_{Ar}H$); 128.8 ($C_{Ar}H$); 128.9 ($C_{Ar}H$); 129.0 ($C_{Ar}H$); 129.4 ($C_{Ar}H$); 129.6 ($C_{Ar}H$); 136.1 (C_{Ar}); 136.1 (C_{Ar}); 138.4 (C_{Ar}); 166.4 (CO). Mass spectrum, *m/z* (I_{rel}, %): 409 $[M]^+$ (1), 182 (31), 131 (11), 121 (22), 104 (18), 91 (100), 77 (40), 65 (11), 51 (11). Found, %: C 67.44; H 5.72; N 3.25. $C_{23}H_{23}NO_6S$. Calculated, %: C 67.46; H 5.66; N 3.42.

Synthesis of Sultams 4a,c-f,h-j (General Method). A solution of 1,2-dibromoethane (0.9 g, 4.8 mmol) in DMF (40 ml) was added during 1.5 h at 55-75°C to a mixture of the appropriate sulfonamide **2a,c-f,h-j** (4 mmol) and potassium carbonate (1.66 g, 12 mmol) in DMF (60 ml) and the mixture was stirred until the end of reaction (check by TLC). The reaction mixture was then diluted with water (150 ml), acidified with conc. HCl to pH ≤2, and extracted with dichloromethane (3×50 ml). The organic phase was washed with 2% HCl (5×80 ml), dried over sodium sulfate, and evaporated to dryness. The product was crystallized from a mixture of diethyl ether and hexane.

Methyl 2-(4-Ethoxycarbonylphenyl)-1,2-thiazolidine-5-carboxylate 1,1-Dioxide (4i) was isolated by chromatography on silica gel, R_f 0.25.

Ethyl 2-Benzyl-1,2-thiazolidine-5-carboxylate 1,1-Dioxide (4j) was isolated by chromatography on silica gel, oil, R_f 0.35. An analytically pure sample was not successfully obtained.

2-Phenyl-1,2-thiazolidine-5-carboxylic Acid 1,1-Dioxide (5a). A 10% KOH solution (2.7 g, 4.8 mmol) was added to a solution of sultam **4a** (1.02 g, 4 mmol) in 50% aqueous methanol (50 ml) and the mixture stirred for 0.5 h. Water (100 ml) was added and the methanol distilled off in vacuum at 30°C on a rotary evaporator. After this, ethyl acetate (70 ml) was added to the aqueous solution and the mixture accurately acidified with 3% HCl to pH ≤2. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2×30 ml). The organic phases were combined, dried over sodium sulfate, and evaporated to dryness. The product was recrtystallized from a mixture of diethyl ether and hexane. Yield was 92%; mp 137-138°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.54-2.73 (2H, m, H-4); 3.72-3.82 (2H, m, H-3); 4.47 (1H, t, *J* = 8.4, H-5); 7.14-7.36 (5H, m, ArH). ^{13}C NMR spectrum, δ, ppm: 21.6 (C-4); 44.4 (C-3); 62.4 (C-5); 119.4 (*o*-C_{Ar}); 124.0 (*p*-C_{Ar}); 128.9 (*m*-C_{Ar}); 137.8 (*ipso*-C_{Ar}); 164.9 (CO). Mass spectrum, *m/z* (I_{rel}, %): 241 $[M]^+$ (31), 132 (58), 105 (100), 77 (65), 51 (20). Found, %: C 49.64; H 4.61; N 6.08. $C_{10}H_{11}NO_4S$. Calculated, %: C 49.78; H 4.60; N 5.81.

Synthesis of Sultams 6a,e (General Method). A solution of 1-bromo-3-chloropropane (0.75 g, 4.8 mmol) in DMF (60 ml) was added during 1.5 h to a mixture of sulfonamide (**2a** or **2e**) (4 mmol) and potassium carbonate (1.66 g, 12 mmol) in DMF (60 ml) at 60°C. After this the reaction mixture was stirred until the end of the reaction (check by TLC). The reaction mixture was processed as for sultams **4a-f**.

Methyl 2-(2,6-Dimethylphenyl)-1,2-thiazepane-7-carboxylate 1,1-Dioxide (7e). A solution of 1,4-dibromobutane (0.91 g, 4.2 mmol) in DMF (60 ml) was added during 1.5 h to a mixture of sulfonamide **2e** (1.03 g, 4 mmol) and potassium carbonate (1.66 g, 12 mmol) in DMF (60 ml) at 70°C, and the reaction mixture was stirred for 100 h. The mixture was diluted with water (150 ml), acidified with conc. HCl to pH ≤2, and extracted with dichloromethane (3×50 ml). The organic phase was washed with 2% HCl (5×80 ml), dried over sodium sulfate, and evaporated to dryness. The product was recrystallized from a mixture of ethyl acetate–hexane.

2-Phenyl-1,2-thiazinan-6-carboxylic Acid 1,1-Dioxide (8a) was obtained analogously to compound **5a**. Yield was 94%; mp 141-142°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.96 (2H, m, H-4); 2.40 (2H, m, H-5); 3.45 (1H, m, H-3); 3.91 (1H, m, H-3'); 4.15 (1H, t, *J* = 7.3, H-6); 7.24-7.40 (5H, m, ArH). ^{13}C NMR spectrum, δ, ppm : 22.5 (CH_2); 27.6 (CH_2); 52.8 (C-3); 63.6 (C-6); 126.5 (*p*-C_{Ar}); 126.6 (*o/m*-C_{Ar}); 128.6 (*m/o*-C_{Ar}); 140.8 (*ipso*-C_{Ar}); 165.7 (CO). Mass spectrum, *m/z* (I_{rel}, %): 255 $[M]^+$ (13), 146 (50), 119 (50), 104 (58), 91 (25), 77 (100), 65 (17), 50 (40), 39 (40). Found, %: C 51.75; H 4.95; N 5.87. $C_{10}H_{11}NO_4S$. Calculated, %: C 51.75; H 5.13; N 5.49.

(N-Benzylaminosulfonyl)acetic Acid (9j). Sodium hydride (100 mg, 2.5 mmol, 60% dispersion in oil) was added during 0.5 h to a solution of sulfonamide **2j** (0.26 g, 1 mmol) and dibromoethane (0.21 g, 0.96 mmol) in THF (20 ml). After this the reaction mixture was evaporated to dryness in vacuum on a rotary evaporator at 30°C. Diethyl ether (30 ml) and 5% hydrochloric acid (50 ml) were added to the residue. The organic layer was separated, and the aqueous extracted with ethyl acetate (2×25 ml). The organic phases were combined, dried over sodium sulfate, and evaporated. The product was recrystallized from a mixture of ethyl

acetate and hexane. Yield was 92%; mp 155-156°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.05 (2H, s, SO_2CH_2); 4.19 (2H, d, *J* = 6.5, NCH_2); 7.24-7.35 (5H, m, ArH); 7.93 (1H, t, *J* = 6.5, NH). ^{13}C NMR spectrum, δ, ppm: 46.4 ($NHCH_2$); 56.9 (SO_2CH_2); 126.9 (*p*-C_{Ar}); 127.6 (*o/m*-C_{Ar}); 128.0 (*m/o*-C_{Ar}); 137.9 (*ipso*-C_{Ar}); 164.6 (CO). Mass spectrum, *m/z* (I_{rel}, %): 229 $[M]^+$ (5), 210 (10), 106 (100), 91 (50), 77 (18). Found, %: C 47.32; H 5.02; N 6.16. $C_9H_{11}NO_4S$. Calculated, %: C 47.15; H 4.84; N 6.11.

4-Methoxycarbonyl-2-phenyl-1,2,4,5-tetrahydrobenzo[*d*][1,2]thiazepine 3,3-Dioxide (10a). A solution of 1,2-bis(bromomethyl)benzene (1.58 g, 6 mmol) in DMF (40 ml) was added during 2 h to a mixture of sulfonamide **2a** (0.91 g, 4 mmol) and potassium carbonate (1.66 g, 12 mmol) in DMF (60 ml) at 65°C. The mixture was stirred until the end of the reaction (check by TLC). The mixture was diluted with water (150 ml), acidified with conc. HCl to pH ≤2, and extracted with dichloromethane (3×50 ml). The organic phases were combined, washed with 2% HCl (5×80 ml), and evaporated to dryness. The product was recrystallized from ethyl acetate.

Methyl 1-(N-Methyl-N-phenylaminosulfonyl)cyclopropanecarboxylate (11b). A solution of 1,2-dibromoethane (1.65 g, 7.7 mmol) in DMF (40 ml) was added during 2 h to a mixture of sulfonamide **2b** (1.94 g, 8 mmol) and potassium carbonate (3.31 g, 24 mmol) in DMF (60 ml) at 65°C, and the mixture was stirred for a further 24 h. The reaction mixture was then diluted with water (150 ml), acidified with conc. HCl to pH ≤2, and extracted with dichloromethane (3×50 ml). The organic phases were combined, washed with 2% HCl (5×80 ml), dried over sodium sulfate, and evaporated to dryness. Yield was 72%, light-yellow oil. ^{1}H NMR spectrum, δ, ppm: 1.45 (4H, m, CH_2CH_2); 3.51 (3H, s, NCH_3); 3.79 (3H, s, OCH_3); 7.30-7.40 (5H, m, ArH). ^{13}C NMR spectrum, δ, ppm: 17.11 (CH_2CH_2); 40.70 (NCH_3); 40.96 (SO_2C); 53.00 (OCH_3), 126.67 (*o/m*-C_{Ar}); 127.79 (*p*-C_{Ar}); 129.35 (*m/o*-C_{Ar}); 141.48 (*ipso*-C_{Ar}); 168.27 (CO). Mass spectrum, *m/z* (I_{rel}, %): 269 $[M]^+$ (12), 106 (100), 77 (53), 51 (12), 39 (25). Found, %: C 53.70; H 5.62; N 5.26. $C_{12}H_{15}NO_4S$. Calculated, %: C 53.52; H 5.61; N 5.20.

1-(N-Methyl-N-phenylaminosulfonyl)cyclopropanecarboxylic Acid (12b). A 10% solution of KOH (2.8 g, 5 mmol) was added to a boiling solution of ester **8b** (1.07 g, 4 mmol) in 50% aqueous ethanol (20 ml). The solution was heated for a further 10 min, cooled to room temperature, diluted with water (100 ml), and acidified with HCl to pH ≤2. The obtained suspension was extracted with ethyl acetate (3×50 ml), the organic phases were combined, dried over sodium sulfate, and evaporated to dryness. The product was recrystallized from a hexane–ethyl acetate mixture. Yield was 86%; mp 150-151°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.24 (4H, m, CH_2CH_2); 3.43 (3H, s, NCH_3); 7.27-7.37 (5H, m, ArH). ^{13}C NMR spectrum (acetone-d_6), δ, ppm: 14.4 (CH_2CH_2); 38.6 (NCH_3); 39.0 (SO_2C); 125.9 (*p*-C_{Ar}), 126.1 (*o/m*-C_{Ar}); 127.6 (*m/o*-C_{Ar}); 140.4 (*ipso*-C_{Ar}); 167.0 (CO). Mass spectrum, *m/z* (I_{rel}, %): 255 (32) $[M]^+$, 106 (100), 79 (21), 77 (62), 51 (12), 39 (44). Found, %: C 51.70; H 5.22; N 5.56. $C_{11}H_{13}NO_4S$. Calculated, %: C 51.75; H 5.13; N 5.49.

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