SYNTHESIS OF 2-ALKYL-1-ALLYL-3-ARYLSULFONYL-ISOTHIOUREAS*

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2-Alkyl-1-allyl-3-arylsulfonyl-isothioureas *III* are not described in the literature. These compounds are valuable intermediate products for new potentially bioactive sulfonamide derivatives. The title compounds *III* (see Table I) can be prepared from 1-allyl-3-arylsulfonyl-thioureas *I* (refs[1,2]) with monohalogen alkanes under alkaline conditions (method *A*) or from N-arylsulfonyl-iminothiocarbonic acid ester chlorides *II* (ref.[3]) with excess allylamine (method *B*). Because of the small number of compounds *II* being known only a few representatives *III* have been made via this easy reaction route. The yields by method *B* (listed in Table I) are usually higher than by method *A* and the products are of high purity.

It was already reported that representatives of N-arylsulfonyl-isothioureas tend to form polymorphes (refs[4,5]). Such polymorphic species were shown to exist for *IIIc* and *IIIk*. Some solids exhibit considerably different IR spectra. The ν(NH) absorption band is found in the region between 3 270 and 3 370 cm^{-1} . The ν(C=C) of the allyl group can be detected as a weak band between 1 648 and 1 630 cm^{-1} in any compound. Deuteration experiments show clearly that the strong band between 1 600 and 1 500 cm^{-1} is influenced very much by coupling effects, within the N=C(S–R)NH moiety. In agreement with investigations of structurally similar compounds (ref.[6]) we think that the $\nu_{as}(SO_2)$ is located between 1 290 and 1 240 cm^{-1} while the corresponding symmetric mode is found below 1 145 cm^{-1} . This is in accordance with ref.[7] for compounds with a sulfonylimino structure.

The EI mass spectrometric structural analysis of the four 2-substituted 1-allyl-3-tosyl-isothioureas *IIId*, *IIIf*, *IIIg* and *IIIi* (see Table II) shows that the fragmentation pathways are in agreement with the structure of the compounds *III* and prove a uniform fragmentation path which is only slightly influenced by the substituents R^2. In order to study the influence of the substituents R^1 and/or R^2 on the ^{13}C chemical shifts in the

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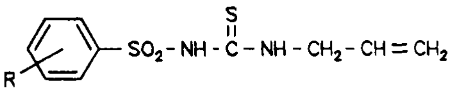
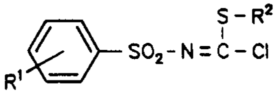
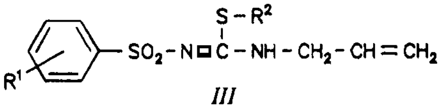
N=C(SR^2)NH-sequence the ^{13}C NMR spectra of the compounds *III* have been recorded (see Table III). The investigation shows no significant shift of this ^{13}C signal. Hence for the compounds *III* a signal at 169.2 ± 1.0 ppm appears to be characteristic of the carbon atom of this isothiourea sequence. The chemical shifts found for the carbon atoms of the arylsulfonyl group are in good agreement with results of other arylsulfonyl derivatives (ref.[8]).



Ia, R = H
Ib, R = 4-CH_3
Ic, R = 4-Br
Id, R = 2-Cl
Ie, R = 4-Cl
If, R = 3-NO_2



IIa, R^1 = H; R^2 = CH_3
IIb, R^1 = 4–CH_3; R^2 = CH_3
IIc, R^1 = 4–CH_3; R^2 = C_2H_5
IId, R^1 = 2–Cl; R^2 = CH_3
IIe, R^1 = 4–Cl; R^2 = CH_3



III

	R^1	R^2
a	H	CH_3
b	H	C_2H_5
c	4-CH_3	CH_3
d	4-CH_3	C_2H_5
e	4-CH_3	$CH_2CH_2CH_3$
f	4-CH_3	$CH(CH_3)_2$
g	4-CH_3	$CH_2CH=CH_2$
h	4-CH_3	$(CH_2)_3CH_3$
i	4-CH_3	$CH_2C_6H_5$
k	4-CH_3	$CH_2C_6H_4NO_2(4)$
l	4-Br	C_2H_5
m	4-Br	$CH_2CH=CH_2$
n	2-Cl	CH_3
o	2-Cl	C_2H_5
p	4-Cl	CH_3
q	4-Cl	C_2H_5
r	4-Cl	$CH_2CH=CH_2$
s	3-NO_2	CH_3
t	3-NO_2	$CH_2C_6H_5$

TABLE I

Yields, melting points and analytical data of compounds *IIIa* – *IIIt*

Compound	Educts	Yield, % Method	M. p., °C	Formula (M. w.)	Calculated/Found	
					% N	% S
IIIa	*Ia* + CH_3I	42/*A*	55 – 57	$C_{11}H_{14}N_2O_2S_2$	10.36	23.72
	IIa + CH_2=$CHCH_2NH_2$	82/*B*		(270.4)	10.01	23.55
IIIb	*Ia* + C_2H_5I	71/*A*	59 – 61	$C_{12}H_{16}N_2O_2S_2$	9.85	22.56
				(284.4)	10.16	22.40
IIIc	*Ib* + CH_3I	52/*A*	62[a]	$C_{12}H_{16}N_2O_2S_2$	9.85	22.56
	IIb + CH_2=$CHCH_2NH_2$	84/*B*		(284.4)	9.44	22.10
IIId	*Ib* + C_2H_5I	76/*A*	87 – 89	$C_{13}H_{18}N_2O_2S_2$	9.39	21.49
	IIc + CH_2=$CHCH_2NH_2$	78/*B*		(298.4)	9.73	21.89
IIIe	*Ib* + $CH_3CH_2CH_2Br$	78/*A*	73 – 75	$C_{14}H_{20}N_2O_2S_2$	8.97	20.52
				(312.5)	9.28	20.49
IIIf	*Ib* + $(CH_3)_2CHBr$	51/*A*	83 – 84	$C_{14}H_{20}N_2O_2S_2$	8.97	20.52
				(312.5)	9.05	19.97
IIIg	*Ib* + CH_2=$CHCH_2Br$	68/*A*	72 – 74	$C_{14}H_{18}N_2O_2S_2$	9.02	20.66
				(310.5)	9.36	20.59
IIIh	*Ib* + $CH_3(CH_2)_3Br$	31/*A*	46 – 48	$C_{15}H_{22}N_2O_2S_2$	8.58	19.64
				(326.5)	9.02	19.53
IIIi	*Ib* + $C_6H_5CH_2Cl$	83/*A*	103 – 105	$C_{18}H_{20}N_2O_2S_2$	7.77	17.79
				(360.5)	8.05	17.89
IIIk	*Ib* + 4-$NO_2C_6H_4CH_2Br$	83/*A*	153.6[b]	$C_{18}H_{19}N_3O_4S_2$	10.36	15.81
				(405.5)	10.72	15.62
IIIl	*Ic* + C_2H_5I	72/*A*	119 – 121	$C_{12}H_{15}BrN_2O_2S_2$	7.71	17.65
				(363.3)	8.19	17.42
IIIm	*Ic* + CH_2=$CHCH_2Br$	68/*A*	72 – 74	$C_{13}H_{15}BrN_2O_2S_2$	7.46	17.09
				(375.3)	7.56	16.63
IIIn	*Id* + CH_3I	56/*A*	61 – 63	$C_{11}H_{13}ClN_2O_2S_2$	9.19	21.04
	IId + CH_2=$CHCH_2NH_2$	73/*B*		(304.8)	8.92	21.19
IIIo	*Id* + C_2H_5I	57/*A*	69 – 72	$C_{12}H_{15}ClN_2O_2S_2$	8.79	20.11
				(318.9)	8.56	20.56
IIIp	*Ie* + CH_3I	52/*A*	70 – 71	$C_{11}H_{13}ClN_2O_2S_2$	9.19	21.04
	IIe + CH_2=$CHCH_2NH_2$	79/*B*		(304.8)	9.02	20.84

TABLE I
(*Continued*)

Compound	Educts	Yield, % Method	M. p., °C	Formula (M. w.)	Calculated/Found % N	Calculated/Found % S
IIIq	*Ie* + C_2H_5I	65/*A*	97 – 99	$C_{12}H_{15}ClN_2O_2S_2$ (318.9)	8.79 8.59	20.11 19.97
IIIr	*Ie* + $CH_2{=}CHCH_2Br$	68/*A*	84 – 86	$C_{13}H_{15}ClN_2O_2S_2$ (330.9)	8.47 8.83	19.38 19.30
IIIs	*If* + CH_3I	75/*A*	89 – 91	$C_{11}H_{13}N_3O_4S_2$ (315.4)	13.32 13.47	20.33 19.99
IIIt	*If* + $C_6H_5CH_2Cl$	56/*A*	98 – 101	$C_{17}H_{17}N_3O_4S_2$ (391.5)	10.73 11.04	16.38 16.18

[a] Modification A, crystallized from ethanol; modification B (m.p. 59 °C) crystallized from benzene. [b] Modification A, crystallized from ethanol; modification B (m.p. 149.6 °C) crystallized from ethanol; modification C (m.p. 110.2 °C), recrystallized from benzene.

TABLE II
Mass spectra (*m/z*; relative intensity, %) of compounds *IIId*, *IIIf*, *IIIg* and *IIIi*

Ions	Compound *IIId*	*IIIf*	*IIIg*	*IIIi*
$M^{+\bullet}$	298/4	312/1	310/<1	360/9
$M - [(R^2)]^+$	269/2	269/3	269/1	269/3
$M - [(R^2SH)]^{+\bullet}$	236/23	236/28	236/11	236/9
$M - [(R^2 + SO_2)]^+$			205/1	205/9[a]
$M - [(R^2SH + SO_2)]^{+\bullet}$	172/1	172/1	172/3	172/2
$M - [(CH_3C_6H_4SO_2)]^+$	143/44	157/68	155/90[a]	205/9[a]
$[R^2SCH{=}NC_3H_5]^+$	129/15	143/7	141/43	191/1
$[CH_3C_6H_4SO_2]^+$	155/92	155/65	155/90[a]	155/39
$[C_7H_7]^+$	91/100	91/100	91/100	91/100
$[C_3H_5NHCN + H]^+$	83/13	83/4	83/4	83/8
$[R^2SH]^+$	62/2	76/–	74/10	124/22
$[C_5H_5]^+$	65/14	65/12	65/13	65/9
$[C_3H_6N]^+$	56/38	56/74	56/10	56/14
$[C_3H_5]^+$	41/11	41/17	41/18	41/3

[a] Sum of two different ions.

TABLE III
^{13}C NMR spectra (ppm, δ-scale) of compounds *IIIb* – *IIIi*, *IIIl*, *IIIo*, and *IIIq*

Compound	Allyl group			Substituent R^2	Arylsulfonyl group				R^1	$\mathrm{N{=}\overset{S}{C}{-}NH}$
	$-CH_2-$	$=CH-$	$=CH_2$		C(1)	C(2,2′)	C(3,3′)	C(4)		
IIIb	46.3	132.1	118.1	26.0 (CH_2); 14.3 (CH_3)	142.5	126.2	128.7	131.6	–	169.3
IIIc	46.3	131.7	117.9	– 14.2 (CH_3)	142.7	126.2	129.3	139.8	21.5	169.5
IIId	46.3	131.8	117.9	25.9 (CH_2); 14.3 (CH_3)	142.7	126.2	129.3	139.8	21.5	169.1
IIIe	46.3	131.8	117.9	33.4 (CH_2); 22.5 (CH_2) 13.2 (CH_3)	142.6	126.3	129.3	139.9	21.5	169.1
IIIf	46.3	131.8	118.0	37.5 (CH); 22.9 ($2CH_3$)	142.7	126.3	129.3	139.9	21.5	169.0
IIIg	46.4	131.7	118.0	34.2 (CH_2); 132.2 (CH); 119.0 ($=CH_2$)	142.8	126.3	129.3	139.7	21.5	168.3
IIIi	46.4	131.7	118.1	35.7 (CH_2)[a]	142.7	126.4	129.3	139.7	21.5	168.3
IIIl	46.4	131.5	118.3	26.0 (CH_2); 14.2 (CH_3)	141.7	127.8	132.0	126.9	–	169.6
IIIo	46.5	133.0	118.3	26.0 (CH_2); 14.2 (CH_3)	139.9	129.6 132.4	131.5 126.7	131.6	–	170.2
IIIq	46.4	131.5	118.3	26.0 (CH_2); 14.2 (CH_3)	141.1	127.7	129.0	138.4	–	169.5

[a] Other signals of phenyl moiety: 136.1 C(1); 129.1 C(2.2′); 128.6 C(3,3′); 127.6 C(4).

EXPERIMENTAL

The IR spectra were recorded on a spectrometer Specord 75 IR (Zeiss Jena) in KBr disks. To investigate the melting behaviour of the crystalline phases a DSC-2 instrument (Perkin–Elmer) was used. Mass spectra were obtained at 70 eV on a Finnigan MAT TSQ 70 spectrometer with electron impact ionization. The ^{13}C NMR spectra were measured with a Bruker AM 250 in deuteriochloroform using tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale).

General Procedure for Preparation of Isothiourea Derivatives *IIIa* – *IIIt*

A) To a stirred mixture of 1-allyl-3-arylsulfonyl-thiourea *I* (0.02 mol), ethanol (100 ml) and sodium hydroxide (0.80 g, 0.02 mol) in water (20 ml) an alkyl halide (0.02 mol) is added dropwise. After refluxing for 3 to 4 h the solution is concentrated. During cooling and/or after addition of some drops of water the colorless isothioureas *III* crystallize. In cases of oily products crystallization can be stimulated by rubbing the materials with small amounts of ligroin. Finally the derivatives are recrystallized from diluted ethanol. Data of the elementary analysis are listed in Table I.

B) To a stirred solution of allylamine (1.43 g, 0.025 mol) in acetonitrile (80 ml) a solution of N-arylsulfonyl-iminothiocarbonic acid ester chloride (0.01 mol) in acetonitrile (20 ml) is added dropwise at temperatures below 5 °C. Afterwards the mixture is heated gently to about 50 °C for one hour. The solution is concentrated, the solid amine hydrochloride separated and the solution treated as mentioned under method *A*. For yields see Table I.

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