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REACTION OF HYDRAZINE DERIVATIVES WITH *METHYLSULPHONYL CHLORIDE* SYNTHESIS OF ALKENYLPYRAZOLES

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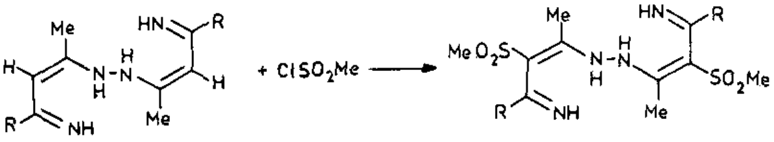
Abstract **The reaction of hydrazine derivatives with methylsulphonyl chloride led to new 2-methylsulphonylhydrazine derivatives which were cyclized to alkenylpyrazoles. The structure of an important product was confirmed by a X-ray analysis.**

Hydrazine derivatives 1 are easily obtained by addition of ketazine dianions to saturated nitriles[1] and are useful starting materials for the synthesis of heterocycles[1,2]. Accordingly, we have thought of interest to study the reaction of hydrazines 1 with methylsulphonyl chloride.

When hydrazine derivatives 1 react with methylsulphonyl chloride at room temperature only products of bis-condesation 3 are isolated (Scheme I).

Scheme I

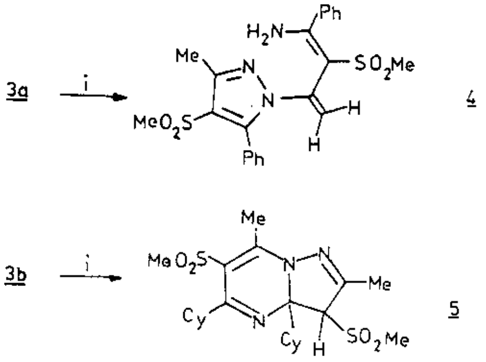


1 2 3

1a , R = Ph
1b , R = Cyclohexyl

Compounds 3 were charaterized on the basis of their microanalytical and spectral data. The ^{1}H nmr spectra show two singlets, corresponding to the CH_3 protons, consistents with the symmetrical structure of compounds 3 . We have studied the behaviour of compounds 3 towards acids. Thus, alkenylpyrazole 4 was obtained in a high yield when a solution of 3a in THF was treated with 2N - H_2SO_4 or under Lewis acid catalysis, whereas, the compound 3b in the same conditions afforded the corresponding 3*H*-pyrazolo[1,5-a]pyrimidine 5 (Scheme II). This different behaviour could be due to a greater conjugation of the product 3a .

Scheme II

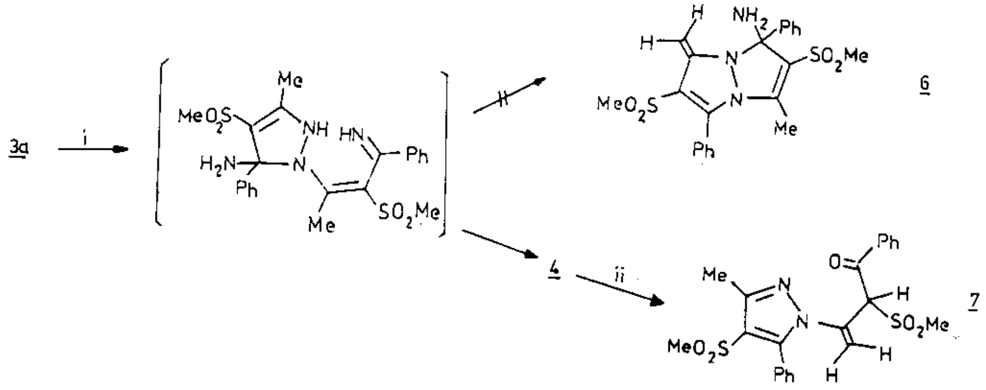


i: 2N H_2SO_4 or $AlCl_3$ Cy = Cyclohexyl

In the ir spectrum of 4 two clear absorptions at 3310 and 3420 (NH_2) cm^{-1} are observed. The ^1H nmr spectrum shows two singlets at ca. δ 4.2 and 4.5 ppm corresponding to a $=CH_2$ grouping. These data are also consistent with the heterocycle 6 (Scheme III).

The formation of 4 can be explained in terms of an intramolecular nucleophilic addition of the enamine nitrogen atom on the imine C=N double bond following the extrusion of an ammonia molecule (Scheme III).

Scheme III



i: 2N H_2SO_4 or $AlCl_3$ ii: 6N H_2SO_4

When the compound 3a was treated with H_2SO_4 in more vigorous conditions, the heterocycle 7 was obtained (Scheme III). Compound 7 displays in its ir spectrum a clear absorption ca. 1675 (C=O) cm^{-1}. In the ^1H nmr spectrum appear two doublets c.a. δ 4.3 and 5.8 ppm which are assigned to the $=CH_2$ grouping.

The structure 4 was unequivocally established by an X-ray single crystal structure analysis.

X Ray Experimental A colorless crystal of approximately 0.33 x 0.10 x 0.09 mm was used during the measurements. Throughout the experiment MoKα radiation was used with a graphite crystal monochromator on a Nonius CAD4 single crystal diffractometer.

The unit cell dimensions were determined from the angular settings of 25 reflections ($\theta > 20°$). The intensity data of 13499 reflections, (one quarter sphere up to $\theta = 30°$), hkl range from (-9,0,0) to

(9,29,41) were measured, using the ω-2θ scan technique, with a variable scan rate with a maximum scan time of 60 seconds per reflection. The intensity of the primary beam was checked throughout the data collection by monitoring three standard reflections every 60 minutes. The final drift correction factors were between 0.989 and 1.035. On all reflections profile analysis was performed[3,4]; empirical absorption correction was applied, using psi-scans[5], μ(MoKα) = 2.61 cm^{-1} (correction factors were in *the range* 0.75 *to* 1.00). Symmetry equivalents reflections were averaged, $R_{int} = \sum(I - \langle I \rangle)/\sum I = 0.040$, resulting in 6469 unique reflections of which 1255 were observed with $I > 3\sigma(I)$. Lorentz and polarization corrections were applied.

The structure was solved by Direct Methods using SHELX 86[6]. The structure was refined by least-squares using SHELX[7]. Atomic scattering factors were taken from the International Tables for X-ray Crystallography[8]. Isotropic least-squares refinement converged at R = 0.11. At this stage an empirical *absorption correction was applied*[9]. *Resulting in a decrease of* R *to* 0.10. *Maximum and minimum* corrections factors were 0.58 and 1.20. Final least-squares refinements involved, positions and anisotropic thermal parameters for all no-hydrogen atoms. Hydrogen atoms, all found by difference Fourier synthesis, were refined as rigid groups riding on their parents atoms, except H091 and H092, bonded to N9, for which positional parameters were refined. Isotropic temperature factors were refined for all hydrogen atoms except for H311, H312 and H313, bonded to C31, which had fixed temperature *factor of* 0.08 *Å*^{2}. *The final conventional agreement factors were* $R = 0.061$ *and* $R_w = 0.059$ *for* 1255 'observed' reflections and 312 variables. The function minimized was $\sum w(Fo-Fc)^2$ with $w = 1/(\sigma^2(Fo) + 0.00040\ Fo^2)$ and σ(Fo) from counting statistics. The maximum shift over error ratio in the last full matrix least-squares cycle was less than 0.43. The final difference Fourier map showed a residual electron density between -0.16 and 0.20 e/Å^3. A summary of crystal data and data collection parameters are given in Table 1. Figure 1, which shows the atomic arrangement and the numbering *was drawn with PLUTO program*[10]. *Geometrical parameters were calculated with* PARST[11]. Final positional and thermal parameters are given in Table 2. The molecular geometry data is collected in Table 3. No unusual geometric features are present in the molecule.

Table 1 : Crystallographic Data

formula	$C_{22}H_{23}N_3O_4S_2$	λ, Å	0.71073
formula weight	457.561	total reflections	13499
crystal size, mm	0.33 x 0.10 x 0.09	unique reflections	6469
space group	P_{bca}	observed reflections	1255 ($I>3\sigma(I)$)
a, Å	7.084(1)	weighting scheme	$1/(\sigma^2(F)+0.0004F^2)$
b, Å	21.166(1)	no. parameters	311
c, Å	29.662(2)	R	0.0608
V, Å	4447.41(6)	R_w	0.0581
T, K	293 K	max. shift/Error	0.430
d exptl., g/cm^3	1.37	h range	-9 - 9
μ(Mo Kα), cm^{-1}	2.61	k range	0 - 29
θ range, °	0-30	l range	0 - 40
diffractometer	CAD4	min and max peaks in final diff map, eÅ^{-3}	-0.16 - 0.20

Table 2 : Fractional Positional and Thermal Parameters (with esd's)

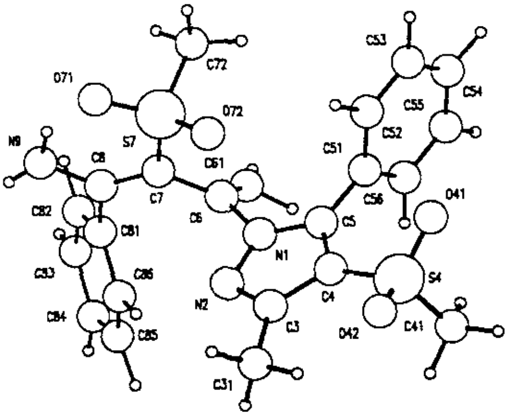
$U_{eq}=1/3\ \sum_i U_{ii}$

Atom	x	y	z	U_{eq}(*100)
S4	0.0179(5)	0.15971(14)	0.32811(10)	4.71(11)
S7	-0.1592(5)	-0.07226(14)	0.44430(10)	4.39(11)
O41	0.0341(12)	0.1913 (3)	0.37058(23)	5.1 (3)
O42	0.1887(13)	0.1459 (4)	0.3056 (3)	7.5 (4)
O71	-0.0790(12)	-0.1328 (4)	0.45518(27)	6.5 (4)
O72	-0.0361(11)	-0.0235 (3)	0.43046(23)	5.1 (3)
N1	-0.2928(13)	0.0170 (4)	0.3608 (3)	4.0 (4)
N2	-0.1961(14)	-0.0111 (4)	0.3263 (3)	4.5 (4)
N9	-0.3586(19)	-0.1948 (5)	0.4118 (4)	5.4 (5)
C3	-0.0846(16)	0.0327 (5)	0.3105 (3)	3.7 (4)
C4	-0.1021(16)	0.0901 (5)	0.3356 (4)	4.2 (4)
C5	-0.2409(15)	0.0776 (5)	0.3682 (3)	3.6 (4)
C6	-0.4174(18)	-0.0221 (5)	0.3868 (4)	3.9 (4)
C7	-0.3396(16)	-0.0805 (5)	0.4049 (3)	3.5 (4)
C8	-0.4176(16)	-0.1382 (5)	0.3951 (3)	3.7 (4)
C31	0.0427(18)	0.0210 (6)	0.2705 (4)	5.9 (5)
C41	-0.1288(26)	0.2057 (6)	0.2945 (5)	8.4 (7)
C51	-0.3172(16)	0.1181 (4)	0.4041 (4)	3.1 (4)
C52	-0.2201(17)	0.1239 (5)	0.4444 (4)	4.5 (5)
C53	-0.2838(21)	0.1627 (5)	0.4784 (4)	5.6 (5)
C54	-0.4500(21)	0.1956 (5)	0.4718 (4)	5.1 (5)
C55	-0.5494(21)	0.1898 (5)	0.4331 (4)	5.6 (5)
C56	-0.4770(16)	0.1514 (5)	0.3985 (4)	4.0 (4)
C61	-0.5919(18)	-0.0035 (5)	0.3946 (4)	4.1 (5)
C72	-0.2738(18)	-0.0442 (6)	0.4932 (4)	4.9 (5)
C81	-0.5763(16)	-0.1446 (4)	0.3632 (4)	3.3 (4)
C82	-0.7451(21)	-0.1698 (5)	0.3778 (4)	5.1 (5)
C83	-0.8965(22)	-0.1780 (6)	0.3498 (5)	6.6 (6)
C84	-0.8740(22)	-0.1603 (7)	0.3042 (5)	6.9 (6)
C85	-0.7108(25)	-0.1326 (7)	0.2901 (4)	7.1 (7)
C86	-0.5581(22)	-0.1256 (6)	0.3177 (4)	5.8 (6)

Table 3 : Bond Lengths (Å) and Bond Angles (°) (with esd's)

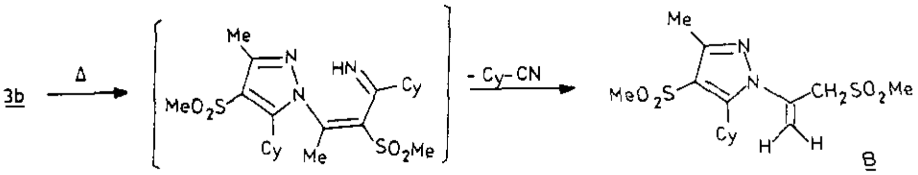
S4 - O41	1.431(7)	C5 - C4	1.404(14)
S4 - O42	1.412(9)	N9 - C8	1.363(13)
S4 - C4	1.717(11)	C8 - C81	1.476(14)
S4 - C41	1.739(13)	C52 - C53	1.377(15)
S7 - O72	1.414(7)	C6 - C61	1.319(15)
S7 - C7	1.741(11)	C56 - C55	1.407(14)
S7 - O71	1.439(8)	C81 - C86	1.414(15)
S7 - C72	1.767(11)	C81 - C82	1.380(15)
N2 - N1	1.368(11)	C4 - C3	1.432(14)
N2 - C3	1.306(12)	C54 - C53	1.383(17)
C7 - C8	1.372(13)	C54 - C55	1.352(15)
C7 - C6	1.456(14)	C3 - C31	1.512(14)
C51 - C5	1.471(14)	C85 - C86	1.365(17)
C51 - C52	1.387(14)	C85 - C84	1.361(17)
C51 - C56	1.345(13)	C82 - C83	1.367(16)
N1 - C5	1.353(12)	C84 - C83	1.414(18)
N1 - C6	1.435(13)		
O41-S4 -O42	116.4(5)	C7 -C8 -N9	125.7(11)
O41-S4 -C4	109.1(5)	C7 -C8 -C81	121.6(10)
O42-S4 -C4	107.9(5)	N9 -C8 -C81	112.7(11)
O41-S4 -C41	106.9(6)	C51-C52-C53	121.6(11)
O42-S4 -C41	110.9(7)	C7 -C6 -N1	117.1(10)
C4 -S4 -C41	105.0(7)	C7 -C6 -C61	123.1(11)
O72-S7 -C7	109.3(5)	N1 -C6 -C61	119.8(11)
O72-S7 -O71	118.2(5)	C51-C56-C55	121.4(11)
C7 -S7 -O71	110.6(5)	C8 -C81-C86	121.1(11)
O72-S7 -C72	106.0(5)	C8 -C81-C82	119.6(10)
C7 -S7 -C72	104.4(6)	C86-C81-C82	119.2(12)
O71-S7 -C72	107.3(6)	S4 -C4 -C5	126.8(9)
N1 -N2 -C3	105.2(8)	S4 -C4 -C3	128.3(9)
S7 -C7 -C8	121.8(8)	C5 -C4 -C3	104.9(9)
S7 -C7 -C6	116.1(8)	C53-C54-C55	121.2(12)
C8 -C7 -C6	121.7(10)	N2 -C3 -C4	111.4(10)
C5 -C51-C52	119.7(10)	N2 -C3 -C31	121.8(10)
C5 -C51-C56	121.8(10)	C4 -C3 -C31	126.8(10)
C52-C51-C56	118.5(10)	C86-C85-C84	122.5(13)
N2 -N1 -C5	113.4(8)	C81-C86-C85	118.0(13)
N2 -N1 -C6	117.3(8)	C81-C82-C83	122.6(12)
C5 -N1 -C6	128.9(9)	C52-C53-C54	118.4(12)
C51-C5 -N1	124.8(10)	C85-C84-C83	120.2(13)
C51-C5 -C4	130.2(10)	C82-C83-C84	117.4(14)
N1 -C5 -C4	105.0(9)	C56-C55-C54	118.9(13)

Fig. 1. Plot, Made with PLUTO (Motherwell, 1976) Showing the Molecular Arrangement and the Atomic Numbering



When heating, compounds 3a and 3b showed a different behaviour again. Thus, 3b led to a new alkenylpyrazole 8 while 3a , in the same conditions afforded the same heterocycle 4 obtained in acidic media.

Scheme IV



In conclusion, hydrazines 1 are suitable starting materials for the preparation of new heterocycles. On the other hand, alkenylpyrazoles, not readily made by conventional routes[12], are easily obtained from the easily available hydrazines 1 .

EXPERIMENTAL

The infrared spectra were recordered on a Pye-unicam SP-1000 using KBr as support. The ^{1}H and ^{13}C nmr spectra were recordered on a Varian FT-80 A and a Brücker AC-300 spectrometers in deuteriochloroform using TMS as internal standard. Chemical shifts are expressed in δ(ppm). The mass spectra were recordered on a Hewlett Packard 5897A and the elemental analysis were performed by Mikroanalytisches Perkin-Elmer 240. All the melting points were determinated on a Büchi apparatus and are uncorrected.

General procedure for 2-methylsulphonyled hydrazine derivatives (3a,b)

To a solution of hydrazine 1 (6 mmol) in THF (50 ml) and triethylamine (18 mmol), methanesulphonyl chloride (12 mmol, THF (50 ml)) was added, with cooling during the addition. After being stirred at room temperature for 12 h, the insoluble salt precipitated was filtered with suction and the resulting solution was evaporated to give 3 after recrystallization in ethanol.

N,N'-Bis-(3-imino-1-methyl-2-methylsulphonyl-3-phenylprop-1-enyl) hydrazine 3a

Yield 1.2g (77%). Mp 236-238°C. Ir (KBr) 1275, 1100 (O=S=O) cm^{-1}.

^{1}H Nmr: 1.33 (s, 3H, CH$_3$), 1.50 (s, NH), 3.13 (s, 3H, CH$_3$), 7.37 (m, 10H, C$_6$H$_5$).

^{13}C Nmr: 21.35 (q), 44.35 (q), 102.74 (s), 128.34-129.93, 137.13 (s), 155.11 (s), 157.41 (s).

Anal. ($C_{22}H_{26}N_4O_4S_2$): Found C, 55.50; H, 5.72; N, 11.41%. Calcd C, 55.67; H, 5.51; N, 11.78%.

N,N'-Bis(3-cyclohexyl-3-imino-1-methyl-2-methylsulphonylprop-1-enyl)hydrazine 3b

Yield 2.4g (82%) Mp. 208-210°C. Ir (KBr) 1270, 1110 (O=S=O) cm^{-1}.

^{1}H Nmr: 1.00-1.90 (m, 22H, C$_6$H$_{11}$), 2.00 (s, 3H, CH$_3$), 3.00 (s, 3H, CH$_3$), 5.70 (m, NH).

^{13}C Nmr: 21.68 (q), 25.12-29.66, 42.97 (q), 100.01(s), 155.04 (s), 161.91 (s).

Anal. ($C_{22}H_{38}N_4O_4S_2$): Found C, 54.37; H, 7.84; N, 11.68%. Calcd C, 54.29; H, 7.87; N, 11.51%.

1-(3-Amino-1-methylene-2-methylsulphonyl-3-phenylprop-2-enyl)-3-methyl-4-methylsulphonyl-5-phenylpyrazole 4

To a solution of 3a (0.47g, 1 mmol) in THF (30 ml), $AlCl_3$ (0.27g, mmol) was added with cooling during the addition. After being stirred at room temperature during 14 h, the mixture was hydrolyzed with ice-water and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), evaporated and the residue was recrystallized from methanol to afford 4 (0.32g, 70%). Mp. 223-225°C. Ir (KBr) 3420, 3310 (NH_2) cm^{-1}.

^1H Nmr: 2.50 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 4.25 (s, 1H, =CH), 4.50 (s, 1H, =CH), 7.20-7.70 (m, 10H, C_6H_5).

^{13}C Nmr: 13.17 (q), 41.27 (q), 44.47 (q), 102.45 (s), 116.93 (t), 119.73 (s), 127.40, 127.71, 127.85, 128.15, 129.19, 129.67, 129.91, 136.42 (s), 144.58 (s), 147.30 (s), 157.73 (s).

Anal. ($C_{22}H_{23}N_3O_4S_2$): Found C, 57.47; H, 5.02; N, 9.30%. Calcd C, 57.75; H, 5.07; N, 9.18%.

Mass spectrum m/z: 457 (M^+).

5,3a-Dicyclohexyl-2,7-dimethyl-3,6-bis(methylsulphonyl)-3*H*-pyrazolo[1,5-a]pyrimidine 5

A solution of 3b (0.33g, 1 mmol) in THF (25 ml) was treated with 6N H_2SO_4 (10 ml) at room temperature during 12 h. The resulting solution was extracted with ether, dried (Na_2SO_4) and evaporated. The residue was crystallized from methanol. Yield 0.39g (83%). Mp. 191-193°C. Ir (KBr): 1600 (C=N), 1300, 1130 (O=S=O) cm^{-1}.

^1H Nmr: 1.00-2.10 (m, 22H, C_6H_{11}), 2.3 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 4.37 (s, 1H, CH).

^{13}C Nmr: 15.90 (q), 17.02 (q), 23.66-42.97, 72.60 (d), 85.27 (s), 150.69 (s), 154.50 (s), 165.09 (s).

Anal. ($C_{22}H_{35}N_3O_4S_2$): Found C, 56.07; H, 7.42; N, 9.19%. Calcd C, 56.26; H, 7.51; N, 8.95%.

Mass spectrum m/z : 469 (M^+).

3-Methyl-1-(1-methylene-2-methylsulphonyl-3-oxo-3-phenylpropyl)-4-methylsulphonyl-5-phenylpyrazole 7

A solution of 3a (0.47 g, 1 mmol) in THF (30 ml) was treated with 6N H_2SO_4 (10 ml) at room temperature during 12 h. The resulting solution was extracted with ether, dried (Na_2SO_4) and evaporated to give 5 (0.4g, 89%) after recrystallization in methanol.

Mp. 188-190 °C. Ir (KBr) 1685 (C=O) cm^{-1}.

^1H Nmr: 2.59 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 4.30 (d, J=1.9 Hz, 1H, HC=), 5.80 (d, J=1.9 Hz, 1H, HC=), 6.66 (s, 1H, CH), 7.37-7.70 and 8.07-8.33 (m, 10H, C_6H_5).

^{13}C Nmr: 13.20 (q), 40.25 (q), 45.71 (q), 70.66 (d), 120.29 (s), 121.12 (t), 127.31 (s), 128.80 (s), 128.82 (d), 129.37 (d), 129.81 (d) 130.38 (d), 133.11 (s), 134.46 (s), 135.19 (d), 145.46 (s), 147.98 (s).

Anal. ($C_{22}H_{22}N_2O_5S_2$): Found C, 57.32; H, 5.09; N, 6.13%. Calcd C, 57.43; H, 5.16; N, 6.09%. Mass spectrum m/z : 459 (M^++1).

5-Cyclohexyl-3-methyl-1-(1-methylene-2-methylsulphonylethyl)-4-methylsulphonylpyrazole 8

A solution of 3b (0.66 g, 2 mmol) in toluene (30 ml) was heated for 120 h at 100°C, then solvent was evaporated and the residue was crystallized from hexane-chloroform to afford 8 (0.44g, 61%). Mp. 152-154 °C. Ir (KBr) 1300, 1110 (O=S=O) cm^{-1}.

^1H Nmr: 1.10-2.20 (m, 11H, C_6H_{11}), 2.40 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 5.38 (d, J=1.3 Hz, 1H, =CH), 5.74 (d, J=1.3 Hz, 1H, =CH).

^{13}C Nmr: 13.29 (q), 24.89 (t), 26.32 (t), 29.99 (t), 37.25 (d), 40.85 (q), 45.80 (q), 59.18 (t), 117.94 (s), 120.23 (t) 133.40 (s), 149.79 (s), 151.54 (s).

Anal. ($C_{15}H_{24}N_2O_4S_2$): Found C, 49.73; H, 6.55; N, 7.81%. Calcd C, 49.98; H, 6.71; N, 7.77%.

Mass spectrum m/z : 360 (M^+).

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