

PHOTOCYCLIZATION OF N-(3-CHLORO-2-BENZO[*b*]THIENOCARBONYL)-N'-MONOSUBSTITUTED THIOUREAS

Peter KUTSCHY, Ján IMRICH, Juraj BERNÁT, Pavol KRISTIAN,
Olga HRITZOVÁ and Thomas SCHÖFFMANN

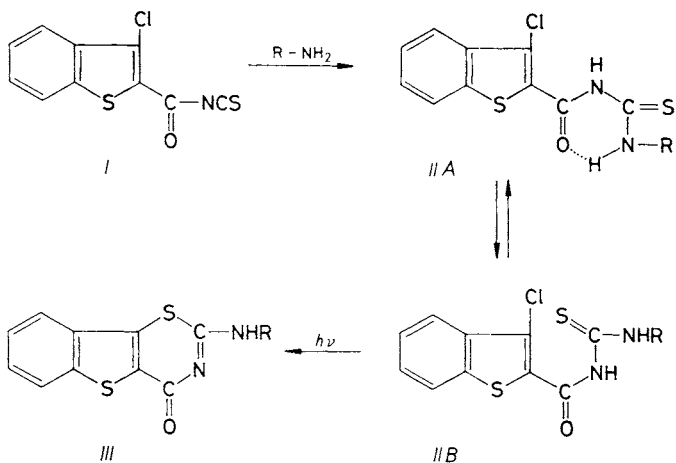
*Department of Organic Chemistry and Biochemistry,
Faculty of Natural Sciences, P. J. Šafárik University, 041 67 Košice*

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N-(3-Chloro-2-benzo[*b*]thienocarbonyl)-N'-monosubstituted thioureas, when irradiated with a high-pressure mercury discharge lamp through a pyrex or quartz filter, give the corresponding benzothienothiazine derivatives in lower yields than the analogous N',N'-disubstituted thioureas. The reactivity lowering of the N'-monosubstituted thioureas is ascribed to the intramolecular hydrogen bond C=O...H—N due to which these compounds in their ground states exist in the six-membered cyclic conformation unfavourable for the cyclization. The photolysis of N'-phenylthiourea results — due to a stronger hydrogen bond — in splitting of the molecule to give 3-chloro-benzo[*b*]thiophene-2-carboxamide and phenyl isothiocyanate.

In our previous papers we dealt with the photocyclizations of N-(3-chloro-2-benzo[*b*]thienocarbonyl)-N',N'-disubstituted thioureas¹ and O-alkyl N-(3-chloro-2-benzo[*b*]thienocarbonyl)monothiocarbamates² giving high yields of the respective benzothienothiazine derivatives. The present paper deals with the above-mentioned photocyclization of N-(3-chloro-2-benzo[*b*]thienocarbonyl)-N'-monosubstituted thioureas (*II*, Table I) prepared by the reaction of 2-isothiocyanatocarbonyl-3-chlorobenzo[*b*]thiophene (*I*) with primary amines (Scheme 1). We have found that the irradiation of thioureas *II* with a high-pressure mercury discharge lamp through a pyrex or quartz filter gives benzothienothiazine derivatives *III* (Table II) in the yields of 35–51%. The structure of the compounds synthesized was confirmed by spectral methods (Tables III and IV). The IR spectra of the thioureas *II* contain the absorption bands of the valence vibrations $\nu(\text{N—H})$ in the region of 3 380 to 3 220 cm^{-1} . The ¹H NMR spectra show the singlets of two NH protons (δ about 10 and 10.40) as well as the expected signals of protons of the benzo[*b*]thiophene nucleus and amine residues. The ¹³C NMR spectrum exhibits typical singlets of thiocarbonyl carbon atoms at δ 178 and those of carbonyl carbon atoms in the region of δ 160. The benzothienothiazine derivatives *III* show the IR spectral absorption bands of the valence vibrations $\nu(\text{C=O})$ in the region of 1 600–1 610 cm^{-1} (*IIIa*, *IIIb*, *IIIc*, *IIIe*) which are shifted — as compared with those of the thioureas — towards lower wavenumbers due to the conjugation of carbonyl group with endocyclic C=N bond. The presence of absorption bands of carbonyl groups at

1 657 and 1 650 cm^{-1} in compounds *IIIc* and *IIIf*, respectively, is probably connected with these compounds being present in their tautomeric imino forms with exocyclic C=N bond³. The ^1H NMR spectra of the cyclization products only exhibit a single signal of the NH proton in the region of δ 9–11. The ^{13}C NMR spectra exhibit – instead of the signal of thiocarbonyl carbon atom – a signal of the carbon atom of C=N double bond in the region of δ 156–162 and also a signal of carbonyl group at δ 163–164. The mass spectrum of compound *IIIa* also agrees with the structure of benzothienothiazine, the main direction of splitting of the molecular ion corresponding to the splitting off of the fragment NCNHC_2H_5 .



In formulae *II, III* : *a*, R = C_2H_5 ; *b*, R = cyclohexyl; *c*, R = $\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$;
d, R = $\text{CH}_2\text{CH}=\text{CH}_2$; *e*, R = $\text{CH}_2\text{C}_6\text{H}_5$

SCHEME 1

The yields of benzothienothiazines *II* are lower than those of the photocyclizations of N',N' -disubstituted thioureas¹ which reach 50–80%. We have found that, at the same conditions of irradiation of N',N' -disubstituted thioureas (λ_{max} 307–313 nm), the reaction time is 1–1.5 h, whereas the N' -monosubstituted thioureas *II* (λ_{max} 305–311 nm) are cyclized more slowly. The reaction time is 9–21 h, when irradiated through quartz, and it is increased to the double with application of the pyrex filter. The photolysis of thioureas *II* produces (regardless of the filter used: pyrex or quartz) besides the main product *III* a complex mixture of side products whose substantial component is of polymeric nature. The low yield of benzothienothiazine and formation of the side products by its subsequent photolysis are not likely, because the

irradiation of *e.g.* the isolated product *IIIa* through quartz causes no change even after 5 h photolysis. These results show that the reactivity differences are caused by different sterical structure of the *N'*-monosubstituted thioureas *II*. It is known⁴ that conformation of starting compounds can affect the course of photochemical reactions. In our case it is presumed that the *N'*-monosubstituted thioureas – in their ground states – are predominantly present in the *IIA* conformation (unfavourable for the cyclization) due to firm intramolecular hydrogen bond between the carbonyl oxygen atom and hydrogen atom of the primary amine residue of thioamide group. On the other hand, the *N',N'*-disubstituted thioureas cannot form such a hydrogen bond and, therefore, their favourable *IIB* conformation is more likely than with the *N'*-monosubstituted thioureas, which can explain their different reactivities. The presumption of the preference of unfavourable *IIA* conformation in the ground state of *N'*-monosubstituted thioureas was confirmed by comparison of IR spectrum of *N*-(3-chloro-2-benzo[*b*]thienocarbonyl)-*N'*-ethylthiourea (*IIa*) with those of model substances, *viz.* *N*-(3-chloro-2-benzo[*b*]thienocarbonyl)-*N',N'*-diethylthiourea (*IV*) and *N*-(3-chloro-2-benzo[*b*]thienocarbonyl)-*N'*-ethyl-*S*-methylisothiourea (*V*) which only contain in their molecules amide and thioamide NH groups, respectively. Compound *IV* shows the absorption band $\nu(\text{N—H})_{\text{free}}$ at $3\,360\text{ cm}^{-1}$, whereas the vibrations of bonded NH group are not observed. Compound *V* only shows the vibrations $\nu(\text{N—H})_{\text{bonded}}$ at $3\,178\text{ cm}^{-1}$, no absorption band

TABLE I
N-(3-Chloro-2-benzo[*b*]thienocarbonyl)-*N'*-monosubstituted thioureas (*II*)

Compound	Molecular formula (<i>M_r</i>)	M.p., °C (solvent)	Yield %	Calculated/found		
				% C	% H	% N
<i>IIa</i>	C ₁₂ H ₁₁ ClN ₂ OS ₂ (298·8)	145–147 (ethanol)	80	48·23	3·71	9·37
				48·38	3·85	9·47
<i>IIb</i>	C ₁₆ H ₁₇ ClN ₂ OS ₂ (352·9)	135–136 (acetone)	63	54·45	4·86	7·93
				54·62	5·01	7·82
<i>IIc</i>	C ₁₈ H ₁₅ ClN ₂ OS ₂ (375·0)	158–160 (acetone)	78	57·66	4·03	7·47
				57·81	3·95	7·70
<i>IId</i>	C ₁₃ H ₁₁ ClN ₂ OS ₂ (310·8)	117–118 (ethanol)	70	50·23	3·57	9·02
				50·30	3·48	8·90
<i>IIe</i>	C ₁₇ H ₁₃ ClN ₂ OS ₂ (360·9)	179–180 (ethanol)	88	56·57	3·36	7·76
				56·61	3·49	7·77
<i>IIf</i>	C ₁₆ H ₁₁ ClN ₂ OS ₂ (346·8)	156–157 (ethanol)	87	55·41	3·20	8·08
				55·63	2·99	8·11

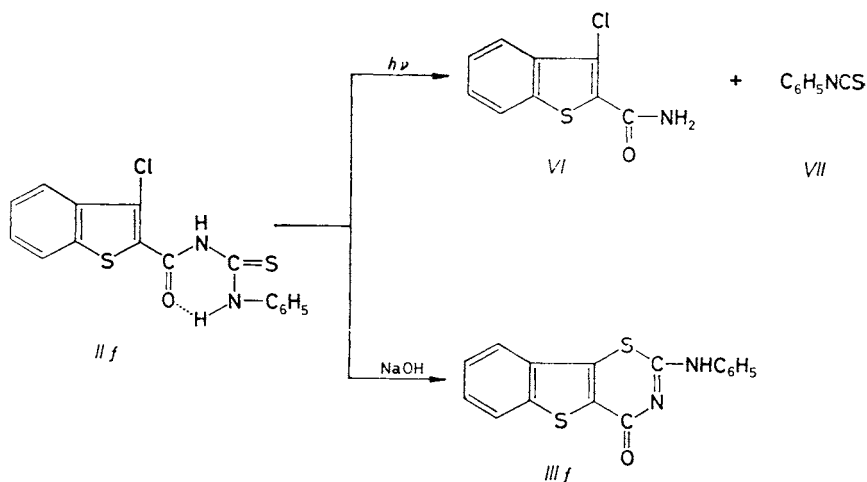
of free NH group being present, which indicates the existence of compound *V* in the six-membered cyclic conformation. Similarly, in the spectrum of thiourea *Ila* there is the absorption band of free NH group at $3\,370\text{ cm}^{-1}$ besides a band at $3\,254\text{ cm}^{-1}$ which was assigned to the bonded NH group. The intensity ratio of these bands is independent of concentration, and no further band of free NH group is observed at low concentrations, which facts confirm the presumption that the *N'*-mono-substituted thioureas in their ground states form six-membered cyclic conformation *Ila* which is fixed by the intramolecular hydrogen bond $\text{C}=\text{O}\dots\text{H}-\text{N}$ and is unfavourable for the cyclization. The given assignment of the $\text{N}-\text{H}$ vibrations also agrees with the fact that the position of the absorption bands $\nu(\text{N}-\text{H})_{\text{free}}$ of the thioureas *II* does not change on substituting the aliphatic amine residue for an aromatic one (Table III), whereas the position of the $\nu(\text{N}-\text{H})_{\text{bonded}}$ band is distinctly affected by such substitution. In the case of *N*-(3-chloro-2-benzo[*b*]thieno-carbonyl)-*N'*-phenylthiourea (*IIf*), the delocalization of free electron pair from nitrogen atom of the phenylamine residue into the aromatic ring causes an acidity increase of the respective proton. The shift of the absorption band $\nu(\text{N}-\text{H})_{\text{bonded}}$ to lower wavenumber ($3\,210\text{ cm}^{-1}$), observed with this compound, indicates a stronger intramolecular hydrogen bond as compared with the other thioureas

TABLE II
2-Substituted 4*H*-benzo[*b*]thieno[2,3-*e*]-1,3-thiazin-4-ones (*III*)

Compound	Molecular formula (M_r)	M.p., °C	Yield %	Irradiation time h	Calculated/found		
					% C	% H	% N
<i>IIIa</i>	$\text{C}_{12}\text{H}_{10}\text{N}_2\text{OS}_2$ (262.4)	266–268	51	14	54.92	3.84	10.68
					54.81	3.99	10.90
<i>IIIb</i>	$\text{C}_{16}\text{H}_{16}\text{N}_2\text{OS}_2$ (316.4)	238–240	47	21	60.73	5.10	8.85
					60.59	5.18	8.71
<i>IIIc</i>	$\text{C}_{18}\text{H}_{14}\text{N}_2\text{OS}_2$ (338.4)	284–286	46	12	63.88	4.17	8.27
					63.99	4.20	8.47
<i>IIId</i>	$\text{C}_{13}\text{H}_{10}\text{N}_2\text{OS}_2$ (274.4)	238–241 (decomposition)	37	9	56.91	3.67	10.21
					57.03	3.55	10.35
<i>IIIe</i>	$\text{C}_{16}\text{H}_{12}\text{N}_2\text{OS}_2$ (324.4)	246–248	35	12	62.94	3.73	8.64
					62.83	3.91	8.80
<i>IIIf</i>	$\text{C}_{16}\text{H}_{10}\text{N}_2\text{OS}_2$ (310.4)	290–292	17	^a	61.90	3.25	9.03
					61.72	3.34	9.21

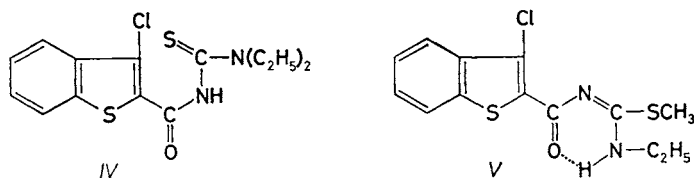
^a Compound *IIIf* was prepared by action of NaOH on thiourea *IIf* in dimethyl sulphoxide.

studied. In accordance therewith, the ^1H NMR spectrum of compound *IIf* shows a down-field shift by more than 2 ppm of the NH proton signal (Table III). The different character of compound *IIf* (λ_{max} 311 nm) – as compared with the other thioureas investigated – makes itself felt also in reactivity. Its irradiation through the pyrex filter gives no benzothienothiazine derivative but gives two other products, viz. 3-chlorobenzo[*b*]thiophene-2-carboxamide (*VI*) and phenyl isothiocyanate (*VII*) (Scheme 2). The structure of amide *VI* was confirmed by independent synthesis



SCHEME 2

starting from 3-chlorobenzo[*b*]thiophene-2-carboxylic acid chloride and ammonia, whereas the phenyl isothiocyanate was identified by converting it into *N,N'*-diphenylthiourea (*VIII*) by the reaction with aniline. Recently, the reaction was described⁵ between 3-chlorobenzo[*b*]thiophene-2-carboxamide and phenyl isothiocyanate in the presence of sodium hydroxide in dimethyl sulphoxide to give the sodium salt of thiourea *IIf* whose heating at 80°C gave 2-phenylaminobenzothienothiazine *III f* in the yield of 53%. We tried to realize this reaction by direct action of NaOH on the thiourea *IIf* and obtained the benzothienothiazine *III f* in the yield of 17%. Application of this method to or action of lithium or sodium hydride on the



other thioureas studied (in the medium of dimethyl sulphoxide or dimethylformamide) produced complex mixtures of products which could not be identified.

EXPERIMENTAL

The infrared absorption spectra were measured with a Specord IR-75 (Zeiss Jena) spectrophotometer in chloroform (*IIa–IIf*, *V*, *VIII*) or in KBr discs (*IIIa–IIIf*, *VI*), the wavenumber values being given in cm^{-1} . When studying the hydrogen bonds of compounds *IIa*, *IIf*, *IV*, and *V* we used tetrachloroethylene. The measurements were carried out in a cell of adjustable length (0.05, 0.1, and 0.5 cm) with the concentrations of 0.006–0.27 mol l^{-1} , the maximum absorption being 70–80%. The wavenumbers and intensities of bands are average values of three measurements each (accuracy $\pm 2 \text{ cm}^{-1}$). The ^1H and ^{13}C NMR spectra were measured in deuteriochloroform (*IIa–IIf*) or hexadeuteriodimethyl sulphoxide (*IIIa–IIIf*, *V*, *VI*) using a Tesla BS 487A (80 MHz) and a Tesla BS 567 (23.15 MHz) apparatus, respectively, with tetramethylsilane as the internal standard. The chemical shifts are given in δ values. The UV spectra were measured with a Perkin-Elmer 402 apparatus in ethanol at the concentration of $1 \cdot 10^{-4} \text{ mol l}^{-1}$; positions of the absorption maxima (λ) are given in nm, the values of molar absorption coeffi-

TABLE III
Spectral properties of N-(3-chloro-2-benzo[*b*]thienocarbonyl)-N'-monosubstituted thioureas (*II*)

Compound	IR, cm^{-1}			UV, λ_{max}		^1H NMR, δ		^{13}C NMR, δ	
	NHCS	C=O	N—H	nm	(log ϵ)	C_6H_4	NH	C=O	C=S
<i>IIa</i>	1 506	1 649		207	(3.35)				
				251	(3.30)	7.52	9.93	159.84	178.82
				3 380	(3.30)	7.92	10.38		
<i>IIb</i>	1 506	1 649		207	(3.08)				
				250	(3.07)	7.47	9.87	159.91	177.23
				3 380	(3.08)	7.85	10.35		
<i>IIc</i>	1 510	1 650		208	(3.43)				
				251	(3.29)	7.50	10.06	159.96	178.40
				3 380	(3.30)	7.85	10.40		
<i>IId</i>	1 510	1 653		208	(3.03)				
				250	(2.97)	7.52	10.06	160.33	178.72
				3 383	(2.98)	7.82	10.40		
<i>IIe</i>	1 510	1 650		209	(3.39)				
				251	(3.28)	7.50	10.00	159.86	178.70
				3 380	(3.27)	7.82	10.65		
<i>IIf</i>	1 495	1 650		210	(3.47)				
				258	(3.31)	7.50	10.07	160.18	177.13
				3 376	(3.44)	7.97	12.22		

icients ($\log \epsilon$) in $\text{m}^2 \text{mol}^{-1}$. The mass spectrum of compound *IIIa* was recorded with an LKB 7000 apparatus at the ionisation energy of 70 eV. 3-Chloro-2-isothiocyanatocarbonylbenzo[*b*]-thiophene (*I*)¹ and N-(3-chloro-2-benzo[*b*]thienocarbonyl)-N',N'-diethylthiourea (*IV*)¹ were prepared by known methods.

N-(3-Chloro-2-benzo[*b*]thienocarbonyl)-N'-monosubstituted Thioureas (*IIa–IIf*)

The respective primary amine (12 mmol) was added drop by drop to a solution of 3 g (11.8 mmol) isothiocyanate *I* in 230 ml cyclohexane with stirring. The separated solid was collected by suction after 1 h standing. The product was dried and recrystallized from a suitable solvent (Tables I and III).

2-Substituted 4*H*-Benzo[*b*]thieno[2,3-*e*]-1,3-thiazin-4-ones (*IIIa–IIIe*)

A solution of 3 mmol thiourea *II* in 250 ml acetone was irradiated with a mercury discharge lamp (TQ 150 Original Hanau) through quartz filter in an immersed apparatus equipped with

TABLE IV
Spectral properties of 2-substituted 4*H*-benzo[*b*]thieno[2,3-*e*]-1,3-thiazin-4-ones (*III*)

Compound	IR, cm^{-1}		$^1\text{H NMR}$, δ		$^{13}\text{C NMR}^b$, δ	
	C=N	C=O	C_6H_4	NH	C=O	C=N
<i>IIIa</i>	1 570	1 606	7.75 8.02 8.30	9.10	164.14	161.34
<i>IIIb</i>	1 540	1 605	7.75 8.05 8.32	9.17	164.52	160.71
<i>IIIc</i>	1 540	1 675	7.75 8.05 8.30	9.48	163.84	161.49
<i>III d</i>	1 580	1 609	7.75 8.02 8.32	9.55	164.37	162.05
<i>IIIe</i>	1 580	1 610	7.75 8.02 8.32	9.85	164.52	162.13
<i>III f</i>	1 583	1 650	7.75 8.00 8.30	11.32	162.95	156.83

^a Mass spectrum: m/z (%): 262 (41); 192 (100); 164 (38); ^b the values of $\delta(\text{C}=\text{O})$ and $\delta(\text{C}=\text{N})$ chemical shifts can be mutually interchanged.

a magnetic stirrer and the quartz-jacketed discharge lamp cooled with water for a period of 9–21 h. During the photolysis course and 15 min before its beginning, the reaction mixture was bubbled with nitrogen gas. A precipitate was deposited on the quartz jacket of the discharge lamp during the reaction. Therefore, after every 3 h the photolysis was interrupted and the precipitate was removed. When the starting compound was consumed (detection by TLC), the reaction mixture was filtered to obtain the first portion of the product, and acetone was evaporated from the mother liquor. The semisolid evaporation residue was dissolved in 50 ml chloroform, concentrated to a volume of 10–15 ml, and left to stand overnight in a refrigerator. The separated precipitate of product *III* was collected by filtration, the filtrate was concentrated to a volume of 5 ml and submitted to chromatography on 100 g silica gel (100–240 μm) with benzene–acetone (7 : 1) as the eluent to give the last portion of the product. The individual product portions were combined and recrystallized from ethanol (Tables II and IV).

Photolysis of N-(3-Chloro-2-benzo[b]thienocarbonyl)-N'-phenylthiourea (*IIf*)

A solution of 1 g (2.9 mmol) thiourea *IIf* was irradiated through the pyrex filter at the same conditions as above for 3 h. Acetone was evaporated, and the semisolid residue was perfectly mixed with 50 ml hexane, filtered, and the filtrate, containing phenyl isothiocyanate, was treated with 0.28 g (0.28 ml, 3 mmol) aniline. After standing one day, the reaction mixture deposited 0.21 g (32%) N,N'-diphenylthiourea (*VIII*), m.p. 153–154°C (ethanol–water), ref.⁶ gives m.p. 155°C. IR: 3 350 (N–H free), 3 140 (N–H bonded), 1 470 (NHCS). The above hexane-insoluble portion was dissolved in 10 ml chloroform and submitted to chromatography on 60 g silica gel (100–250 μm) with benzene–acetone (5 : 2) as the eluent to give 0.37 g (60%) 3-chlorobenzo[b]-thiophene-2-carboxamide (*VI*), m.p. 231–233°C (ethanol). For $\text{C}_9\text{H}_9\text{ClNOS}$ (211.6) calculated: 51.08% C, 2.84% H, 6.62% N; found: 51.22% C, 3.01% H, 6.53% N. IR: 1 615 (C=O). ^1H NMR: 7.62–8.35 (m, C_6H_4). ^{13}C NMR: 118.68 (s), 122.34 (s), 125.47 (s), 122.93 (d), 127.11 (d), 132.63 (d), 135.99 (d), and 136.52 (s) (the benzo[b]thiophene skeleton), 161.45 (s, C=O). The compound was identical with the authentic sample⁷ prepared by amination of 3-chlorobenzo[b]-thiophene-2-carbonyl chloride⁸.

2-Phenylamino-4H-benzo[b]thieno[2,3-e]-1,3-thiazin-4-one (*IIIIf*)

A solution of 1 g (2.9 mmol) thiourea *IIf* in 25 ml absolute dimethyl sulphoxide was treated with 0.12 g (3 mmol) powdered sodium hydroxide, heated to 80°C, and stirred at this temperature 4 h. After cooling, the reaction mixture was poured onto 400 ml ice water, the precipitated solid was collected by suction and recrystallized from ethanol.

N-(3-Chloro-2-benzo[b]thienocarbonyl)-N'-ethyl-S-methylisothiourea (*V*)

A suspension of 0.09 g sodium hydride (3.9 mmol) in 10 ml absolute dimethylformamide was treated with 0.89 g (3 mmol) thiourea *IIf* and stirred until the reaction mixture was clear. Then 0.45 g (0.3 ml, 3.2 mmol) methyl iodide was added, and the mixture was stirred 90 min. The reaction mixture was poured onto 200 ml ice water and left to stand in a refrigerator overnight. The separated solid was collected by suction, washed with water, and recrystallized from ethanol to give 0.74 g (80%) product, m.p. 129–130°C. IR: 3 170 (N–H), 1 560 and 1 570 (C=N–C=O). ^1H NMR: 1.43 (t, $J = 7$ Hz, 3 H, CH_3 –C), 2.73 (s, 3 H, CH_3 –S), 3.66 (q, $J = 7$ Hz, 2 H, CH_2), 7.70 and 8.10 (m, m, 4 H, C_6H_4). ^{13}C NMR: 13.34 (q) and 13.71 (q) (CH_3 –C and CH_3 –S), 38.50 (t, CH_2 –N), 167.26 (s) and 170.97 (s) (C=N–C=O).

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