REACTIONS OF SUBSTITUTED 5-NITRO-3-FUROYLTHIOUREAS

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Received March 7, 1995
Accepted November 4, 1995

Some cyclization and cyclocondensation reactions of 1-(5-nitro-3-furoyl)-3-(4-R-phenyl)thioureas **1a**–**1e** (R = H, CH_3, $N(C_2H_5)_2$, Br, CN) were conducted. 6-R-2-(5-Nitro-3-furoylamino)benzothiazoles **2a**–**2c** (R = H, CH_3, Br) were obtained by bromine-induced cyclization of the corresponding thioureas. Reacted with bromoacetone and ω-bromoacetophenone, respectively, the derivatives **1a**–**1e** gave 2-(4-R-phenylimino)-3-(5-nitro-3-furoyl)-4-R^1-4-thiazolines **3a**–**3e** (R = H, CH_3, $N(C_2H_5)_2$, Br, CN; R^1 = CH_3) and **3f**–**3j** (R = H, CH_3, $N(C_2H_5)_2$, Br, CN; R^1 = C_6H_5), respectively. The structure of the compounds synthesized was confirmed by IR, UV, ^{1}H NMR and MS data.
Key words: 5-Nitro-3-furoylthioureas; Cyclocondensation.

As a continuation of our studies of β-substituted furan derivatives[1,2], this paper reports on some cyclization and condensation reactions of 1-(5-nitro-3-furoyl)-3-(4-R-phenyl)thioureas, where R = H, CH_3, $N(C_2H_5)_2$, Br, CN (compounds **1a**–**1e**). 1-(5-Nitro-3-furoyl)-3-(4-cyanophenyl)thiourea (**1e**), whose synthesis has not been reported so far, was prepared, as the remaining derivatives **1a**–**1d**, by reacting 5-nitro-3-furoylisothiocyanate with the corresponding aromatic amine[3].

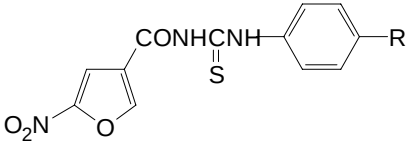
Various arylthioureas are known to undergo intramolecular cyclization to give condensed thiazoles on the action of oxidants. So, 2-aminobenzothiazoles emerge from phenylthiourea on the action of bromine, thionyl chloride, as well as sulfuryl chloride, sulfur(I) chloride, or chlorine[4–7]. Moreover, cyclization of some heterocyclic thioureas is associated with the condensation addition of the thiazole ring to the heteroaromatic ring[8–11].

Within the present work, the three substituted 5-nitro-3-furoylthioureas **1a**, **1b**, **1d** were subjected to bromine-induced cyclization in acetic acid at a slightly elevated temperature to provide the corresponding 6-substituted 2-(5-nitro-3-furoylamino)benzothiazoles **2a**–**2c**. It is clear that the corresponding sulfenyl bromide, as the assumed intermediate product, is an electrophilic agent[10], which directs the electrophilic attack

primarily to the benzene ring rather than to the carbonyl or nitro group of the deactivated furan system.

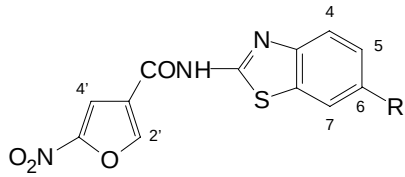
Jurasek and coworkers[12] failed to achieve cyclization of the analogous 3-furoylthioureas having no nitro group in position 5 of the furan system. In our case, it was the nitro group that increased the electrophilic nature of the sulfenyl bromide and promoted the reaction.

2-(4-Substituted phenylimino)-3-(5-nitro-3-furoyl)-4-methyl-4-thiazolines **3a**–**3e** were obtained from the corresponding 5-nitro-3-furoylthioureas **1a**–**1e** and bromo-



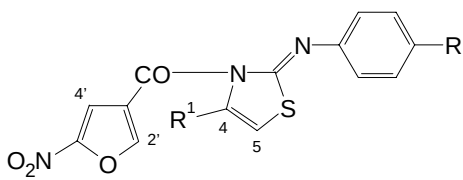
1

	R
a	H
b	CH_3
c	$N(C_2H_5)_2$
d	Br
e	CN



2

	R
a	H
b	CH_3
c	Br



3

	R	R^1
a	H	CH_3
b	CH_3	CH_3
c	$N(C_2H_5)_2$	CH_3
d	Br	CH_3
e	CN	CH_3

	R	R^1
f	H	C_6H_5
g	CH_3	C_6H_5
h	$N(C_2H_5)_2$	C_6H_5
i	Br	C_6H_5
j	CN	C_6H_5

TABLE I

Physico-chemical data of 6-substituted 2-(5-nitro-3-furoylamino)benzothiazoles **2a**–**2c** and substituted 4-thiazolines **3a**–**3j**

Compound	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
2a	242–245[a] 84	$C_{12}H_7N_3O_4S$ (289.3)	49.82 49.67	2.44 2.21	14.53 14.51
2b	218–220[b] 84	$C_{13}H_9N_3O_4S$ (303.3)	51.48 50.96	2.99 3.20	13.86 13.54
2c	227–230[a] 50	$C_{12}H_6BrN_3O_4S$ (368.2)	39.15 39.71	1.64 1.90	11.41 11.74
3a	197–201[c] 77	$C_{15}H_{11}N_3O_4S$ (329.3)	54.70 54.36	3.37 3.52	12.76 11.98
3b	160–162[c] 74	$C_{16}H_{13}N_3O_4S$ (343.3)	55.97 55.91	3.82 3.92	12.24 12.09
3c	178–181[a] 90	$C_{19}H_{20}N_4O_4S$. 0.5 H_2O (409.5)	55.73 55.89	5.17 5.04	13.68 13.11
3d	199–201[c] 79	$C_{15}H_{10}BrN_3O_4S$ (408.2)	44.13 43.82	2.47 2.08	10.29 10.12
3e	236–238[d] 47	$C_{16}H_{10}N_4O_4S$ (354.3)	54.23 53.89	2.84 2.93	15.81 15.98
3f	179–181[c] 68	$C_{20}H_{13}N_3O_4S$ (391.4)	61.37 61.48	3.35 3.49	10.74 10.65
3g	215–217[c] 75	$C_{21}H_{15}N_3O_4S$ (405.4)	62.21 61.84	3.73 3.80	10.36 10.43
3h	208–211[a] 68	$C_{24}H_{22}N_4O_4S$ (462.5)	62.32 62.08	4.80 4.94	12.11 11.57
3i	234–238[c] 69	$C_{20}H_{12}BrN_3O_4S$ (470.3)	51.07 50.12	2.57 2.80	8.93 8.91
3j	252–255[d] 75	$C_{21}H_{12}N_4O_4S$ (416.4)	60.57 60.62	2.91 3.23	13.46 13.56

Recrystallized from: [a] acetic acid; [b] methanol; [c] chloroform–diethyl ether; [d] ethanol.

acetone in ethyl acetate at boil. The corresponding thiazoline hydrobromides were the primary reaction products. These compounds were isolated, and only on alkalinization, the final thiazoline products emerged in 47–90% yields (Table I). The substituted 4-phenyl-4-thiazolines **3f**–**3j** were obtained likewise in 68–75% yields from the thioureas **1a**–**1e** and ω-bromoacetophenone (Table I).

The structure of the newly synthesized compounds was confirmed by elemental and spectral analysis (Tables II–IV). The IR spectra of the derivative series **2** and **3** display, in addition to the characteristic bands, also bands at 1 578–1 520 cm^{-1} and 1 375–1 358 cm^{-1} due to the $\nu(NO_2)_{as}$ and $\nu(NO_2)_s$ vibrations, respectively. For the electronic absorption bands of the benzothiazole series **2** (Table II) corresponding to electronic transitions within the whole conjugated systems of the molecules, bathochromic shifts of 7–19 nm were found relative to the bands of the initial thioureas (the λ_{max} values for **1a**–**1d** are

TABLE II
IR (in KBr) and UV (in dioxane, c = 0.05 mmol l^{-1}) absorption bands of compounds **2a**–**2c** and **3a**–**3j**

Compound	IR spectrum, cm^{-1}		UV spectrum	
	ν(C=O)	ν(C=N)	λ_{max}, nm	log ε
2a	1 682	1 601	305	3.06
2b	1 678	1 610	309	3.19
2c	1 686	1 649	308	3.18
3a	1 581	1 575	340	3.08
3b	1 600	1 570	333	3.28
3c	1 605	1 585	268 340	2.94 2.81
3d	1 680	1 635	343	2.38
3e[a]	1 659	1 612	225 335	3.39 3.28
3f	1 604	1 572	345	3.08
3g	1 603	1 583	345	3.12
3h	1 603	1 577	272 319	2.97 2.75
3i	1 618	1 582	339	3.27
3j[b]	1 606	1581	284 340	3.15 3.37

[a] ν(C≡N) at 2 236 cm^{-1}; [b] ν(C≡N) at 2 218 cm^{-1}.

298, 294, 272, and 289 nm, ref.[3]). For the 4-methyl-4-thiazolines **3a**–**3e** and 4-phenyl-4-thiazolines **3f**–**3j**, the shifts are even more marked, viz. 39–68 and 47–53 nm, respectively.

TABLE III
^{1}H NMR spectral data of compounds **2a**–**2c** and **3a**–**3j**

Compound[a]	H-2′ *J*(2′,4′)	H-4′	H-5[b]	C_4-R[1,c]	Other signals
2a	8.88 d 1.0	8.24 d	–	–	11.7 brs, 1 H (NH); 8.05 dd and 7.83 dd, 2 × 1 H, *J*(4,7) = 6.7 (H-4,H-7); 7.68–7.25 m, 2 H (H-5,H-6)
2b	8.82 d 0.9	8.16 d	–	–	11.5 brs, 1 H (NH); 7.77 brs, 1 H (H-7); 7.66 d and 7.27 d, 1 H and 1 H, *J*(4,5) = 8.0 (H-4,H-5); 2.42 s, 3 H (CH_3)
2c	8.82 1.1	8.18 d	–	–	11.8 brs, 1 H (NH); 8.25 d, 1 H, *J*(7,5) = 1.8 (H-7); 7.70 d, 1 H, *J*(4,5) = 8.7 (H-4); 7.65 dd, 1 H, *J*(5,4) = 8.7, *J*(5,7) = 1.8 (H-5)
3a	7.79 d 1.0	7.45 d	6.45 q	2.08 d	7.75–7.50 m and 7.40–7.20 m, 3 H and 2 H (phenyl)
3b	7.82 d 0.9	7.47 d	6.45 q	2.07 d	7.38 d and 7.16 d, 2 × 2 H, *J* = 8.3 (phenyl); 2.5 s, 3 H (CH_3)
3c	8.04 d 1.0	7.44 d	6.74 q	2.12 d	7.28 m and 6.83 m, 2 × 2 H (phenyl); 3.53 q, 4 H, *J* = 7.1 (N**CH**$_2$CH$_3$); 1.24 t, 6 H, *J* = 7.1 (NCH$_2$**CH**$_3$)
3d	8.19 d 1.0	7.42 d	6.96 q	2.05 d	7.82 d and 7.48 d, 2 × 2 H, *J* = 8.9 (phenyl)
3e	8.22 d 1.0	7.42 d	6.94 q	2.04 d	8.10 d and 7.74 d, 2 × 2 H, *J* = 8.5 (phenyl)
3f	7.86 d 1.0	7.51 d	6.77 s	[d]	7.47–7.04 m, 10 H (2 × phenyl)
3g	7.87 d 1.2	7.51 d	6.75 s	7.34–7.00 m	7.28 d and 7.14 d, 2 × 2 H, *J* = 8.3 (phenyl); 2.38 s, 3 H (CH_3)
3h	8.24 d 1.0	7.61 d	[e]	[e]	7.67–7.05 m, 10 H (2 × phenyl, H-5); 3.60 q, 4 H, *J* = 7.1 (N**CH**$_2$CH$_3$); 0.97 t, 6 H, *J* = 7.1 (NCH$_2$**CH**$_3$)
3i	8.32 d 0.8	7.49 d	7.29 s	7.45–7.13 m	7.65 d and 7.35 d, 2 × 2 H, *J* = 8.7 (phenyl)
3j	8.29 d 1.0	7.50 d	7.30 s	7.49–7.10 m	7.93 d and 7.57 d, 2 × 2 H, *J* = 8.7 (phenyl)

[a] Compounds **2a**–**2c**, **3d**, **3e**, **3h**–**3j** in $(CD_3)_2SO$, compounds **3a**, **3b**, **3f**, **3g** in $CDCl_3$, compound **3c** in $(CD_3)_2CO$; [b] for **3a**–**3j**; [c] $R^1 = CH_3$ for **3a**–**3e**, *J*(CH_3,H-5) = 1.1, $R^1 = C_6H_5$ for **3f**–**3j**; [d] signal present in the multiplet δ 7.47–7.04; [e] signal overlapped by the multiplet of aromatic protons.

The ^{1}H NMR spectra of the nitrofuran substituted benzothiazoles **2a**–**2c** (Table III) exhibit chemical shifts of the H-2′ and H-4′ furan protons within the ranges of δ 8.88–8.82 and δ 8.24–8.16, respectively. The signals are doublets with $J(2',4')$ = 0.9–1.1 Hz. The presence of the benzothiazole ring is confirmed by signals of the corresponding aromatic protons[13]. The furan ring protons of the substituted thiazolines **3a**–**3j** also give doublet signals with $J(2',4')$ interaction constant values of 0.8–1.2 Hz. For the derivatives **3a**–**3e** the H′-2 and H-4′ signals lie in the regions of δ 8.22–7.79 and δ 7.47–7.42, respectively; for the derivatives **3f**–**3j** the corresponding regions are δ 8.32–7.86 and δ

TABLE IV
The EI mass spectra of compounds **2a**–**2c** and **3a**–**3j**

Compound[a]	*m*/*z*, %
2a	289 $M^{+\bullet}$ (30), 243 (52), 216 (13), 215 (100), 187 (16), 150 (27), 140 (77), 105 (8), 96 (8), 94 (100)
2b	303 $M^{+\bullet}$ (29), 257 (59), 229 (100), 201 (27), 164 (29), 163 (18), 140 (67), 106 (17), 94 (39), 77 (21)
2c	369 (20), 367 $M^{+\bullet}$ (20), 323 (29), 321 (29), 295 (35), 293 (35), 230 (33), 228 (33), 140 (100), 94 (50)
3a	330 (20), 329 $M^{+\bullet}$ (100), 283 (32), 236 (67), 217 (24), 189 (18), 140 (53), 118 (21), 94 (24), 77 (27)
3b	343 $M^{+\bullet}$ (77), 297 (29), 236 (100), 231 (21), 203 (21), 140 (37), 132 (29), 94 (20), 91 (36), 65 (17)
3c	400 $M^{+\bullet}$ (98), 385 (71), 354 (100), 261 (57), 260 (55), 246 (59), 236 (61), 164 (50), 145 (41), 140 (34), 133 (35)
3d	409 (39), 407 $M^{+\bullet}$ (38), 297 (11), 295 (11), 236 (100), 198 (14), 196 (14), 157 (12), 155 (13), 140 (71), 94 (28)
3e	355 (12), 354 $M^{+\bullet}$ (58), 308 (26), 242 (16), 236 (37), 143 (16), 141 (11), 140 (100), 102 (18), 94 (22)
3f	392 (25), 391 $M^{+\bullet}$ (100), 390 (53), 345 (33), 298 (43), 251 (29), 180 (24), 140 (35), 134 (17), 77 (57)
3g	405 $M^{+\bullet}$ (100), 404 (46), 359 (36), 298 (98), 265 (55), 194 (48), 140 (44), 94 (39), 91 (85), 65 (73)
3h	462 $M^{+\bullet}$ (79), 447 (46), 416 (44), 323 (48), 322 (65), 308 (37), 298 (34), 164 (37), 140 (34), 105 (100), 72 (97)
3i	471 (49), 469 $M^{+\bullet}$ (48), 299 (17), 298 (100), 141 (14), 140 (54), 134 (19), 105 (30), 94 (25), 77 (29)
3j	417 (16), 416 $M^{+\bullet}$ (56), 415 (18), 370 (30), 298 (27), 276 (16), 140 (100), 134 (15), 102 (23), 94 (34)

[a] For each compound 10 most abundant peaks are given.

7.61–7.49, respectively. The signals of the methyl group in the thiazoline position C-4 (compounds **3a**–**3e**) are doublets at δ 2.12–2.04, those of the H-5 proton are broad quadruplets with $J(CH_3,H\text{-}5)$ = 1.1 Hz.

The molecular ion peaks in the EI mass spectra of the compounds **2a**–**2c** (Table IV) are medium intensity. Their basic fragmentation route is through the splitting of the C–N bond in the β position with respect to the furan ring. An ion with *m/z* 140 forms on charge localization at the fragment containing the furan ring. On the other side is the formation of the fragment ion containing the benzothiazole system, accompanied by hydrogen rearrangement. Additional intense fragment ion peaks emerge from the splitting-off of the $^{\bullet}NO_2$ radical from the molecular ions and subsequent double consecutive elimination of the neutral CO molecule. The EI mass spectra of the derivatives **3a**–**3j** exhibit intense peaks of the molecular ions. Fragment ions which are of interest as they can prove the structure of the compounds are formed from the molecular ions by splitting of the C–N bond in the β position with respect to the furan ring; localization is possible at both of the emerging fragments. The relative intensities of the fragment ions depend appreciably on the substituents R and R^1. Another important route of $M^{+\bullet}$ fragmentation consists in the splitting of the bond in the β position with respect to the substituted benzene ring, accompanied by a rearrangement of two hydrogen atoms to the spitting-off neutral $H_2N–C_6H_4–R$ fragment. For the compounds **3b**, **3d** and **3i**, such ions give the major peaks in the spectra.

EXPERIMENTAL

The melting temperatures were determined on a heated Kofler stage. Infrared spectra were recorded on an FTIR PU 9800 spectrophotometer (Philips), UV spectra (λ, nm; ε, $m^2\ mol^{-1}$), on a Specord UV-VIS M-40 instrument (Zeiss, Jena). ^1H NMR spectra (δ, ppm; *J*, Hz) were scanned on a Tesla BS 587 spectrometer (80 MHz) using tetramethylsilane as the internal standard. EI mass spectra were measured on an MS 902 S instrument (A. E. I. Manchester) using a direct injection system at an electron energy of 70 eV, trap current 100 μA, ion source temperature 175–180 °C for compounds of the series **2** and 145–180 °C for compounds of the series **3**.

The 1-(5-nitro-3-furoyl)-3-(4-substituted phenyl)thioureas **1a**–**1d** were prepared by reacting 5-nitro-furoylisothiocyanate with the corresponding *p*-substituted anilines[3].

1-(5-Nitro-3-furoyl)-3-(4-cyanophenyl)thiourea (**1e**)

Over a period of 15 min, a solution of 4-aminobenzonitrile (2.1 g, 17.8 mmol) in anhydrous diethyl ether was added to a stirred solution of 5-nitro-3-furoylisothiocyanate (3.5 g, 17.6 mmol) in the same solvent at 5–10 °C. The reaction mixture was stirred for another 3 h at the same temperature and allowed to stand for 12 h at room temperature. The solid was then filtered out: yield 4.5 g (81%), m.p. 172–175 °C (ethanol). For $C_{13}H_8N_4O_4S$ (316.3) calculated: 49.36% C, 2.55% H, 17.72% N, 10.14% S; found: 49.65% C, 2.32% H, 17.20% N, 10.35% S. IR spectrum (KBr), cm^{-1}: 2 228 (CN), 1 692 (CO), 1 536 $(NO_2)_{as}$, 1 370 $(NO_2)_s$. UV spectrum (dioxane): 287 (2.92). ^1H NMR spectrum (CD_3SOCD_3): 11.31 s and 10.79 s, 2 × 1 H (NH); 8.86 d, 1 H, *J*(2,4) = 0.9 (H-2′); 8.18 d, 1 H, *J*(4,2) = 0.9 (H-4′); 7.80 bs, 4 H (4-cyanophenyl).

6-Substituted 2-(5-Nitro-3-furoylamino)benzothiazoles **2a**–**2c**. General Procedure

A stirred suspension of the corresponding 1-(5-nitro-3-furoyl)-3-(4-substituted phenyl)thiourea **1a**, **1b**, **1d** (1 mmol) in glacial acetic acid (15 ml) was heated to 60 °C. Bromine (0.16 g, 1.1 mmol) in the same acid (2 ml) was added slowly to the solution and the reaction mixture was stirred for another 2 h without heating. The solid which separated was filtered out, washed with acetic acid and diethyl ether and recrystallized from a suitable solvent. The yields, melting temperatures and results of elemental analysis are given in Table I, the spectral characteristics are included in Tables II–IV.

2-(4-Substituted Phenylimino)-3-(5-nitro-3-furoyl)-4-methyl-4-thiazolines **3a**–**3e**

To a heated solution of the corresponding 5-nitro-3-furoylthiourea **1** (1 mmol) in ethyl acetate (15 ml) was added a single portion of a solution bromoacetone (0.14 g, 1 mmol) in the same solvent (10 ml). The stirred reaction mixture was heated at the boiling temperature for 3 h. The solvent was partly distilled off and the thiazoline hydrobromide was isolated, suspended in water, and alkalinized gently with an aqueous solution of sodium hydrogen carbonate to pH 8. The solid was filtered out at a reduced pressure and recrystallized from a suitable solvent. The yields, melting temperatures, solvents used, and results of elemental analysis are given in Table I, the spectral characteristics are included in Tables II–IV.

2-(4-Substituted Phenylimino)-3-(5-nitro-3-furoyl)-4-phenyl-4-thiazolines **3f**–**3j**

The compounds were prepared as above from the corresponding 5-nitro-3-furoylthiourea **1** (1 mmol) and ω-bromoacetophenone (0.2 g, 1 mmol). The yields, melting temperatures, and results of elemental analysis are given in Table I, the spectral characteristics are included in Tables II–IV.

REFERENCES

1. Stetinova J., Jurasek A., Kovac J., Dandarova M., Rajniakova O.: Collect. Czech. Chem. Commun. *51*, 2186 (1986).
2. Stetinova J., Lesko J., Dandarova M., Kada R., Koren A.: Collect. Czech. Chem. Commun. *59*, 2721 (1994).
3. Jurasek A., Stetinova J., Kovac J., Zvak V., Lesko J., Dandarova M., Vlnieskova E.: Collect. Czech. Chem. Commun. *54*, 699 (1989).
4. Hunter R. F.: J. Chem. Soc. *127*, 2023 (1925).
5. Veltman R. P.: Ukr. Khim. Zh. *22*, 363 (1956); Chem. Abstr. *51*, 4358 (1957).
6. Iwakura Y., Kurita K.: Bull. Chem. Soc. Jpn. *43*, 2535 (1970); and references therein.
7. Metzger J., Plank H.: Chim. Ind. (Milan) *75*, 929, 1260 (1956); Chem. Abstr. *51*, 4358 (1957).
8. Grehn L., Lindberg H.: Chem. Scr. *11*, 199 (1977).
9. Uher M., Lesko J. Toth J.: Collect. Czech. Chem. Commun. *51*, 1678 (1986).
10. Grehn L.: J. Heterocycl. Chem. *15*, 81 (1978).
11. Barnikov G., Boedeker J.: J. Prakt. Chem. *313*, 1148 (1971).
12. Jurasek A., Safar P., Zvak V.: Chem. Papers *41*, 693 (1987).
13. Pretsch E., Clerc T., Seibl J. Simon W: *Tabellen zur Strukturaufklärung organischer Verbindungen*, p. H 325. Springer, Berlin–Heidelberg 1981.