Reactions of bromoacetyl derivatives of furoxan and furazan with S-nucleophiles

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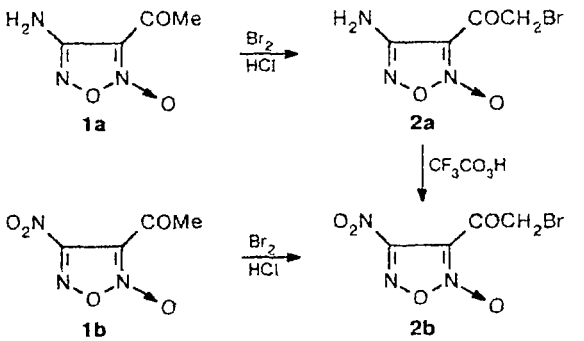
Hetarylthioacetyl- and (2-aminothiazol-4-yl)furoxans and the corresponding furazans unknown previously were synthesized by the reactions of substituted bromoacetylfuroxans and -furazans with hetarylthiols and thiourea, respectively.

Key words: bromoacetylfuroxans, bromoacetylfurazans; hetarylthioacetylfuroxans, hetarylthioacetylfurazans; aminothiazoles; nucleophilic substitution; thiols, cyclization.

In recent years, the interest in 1,2,5-oxadiazole 2-oxide (furoxan) derivatives has markedly increased. This is associated with the ability of furoxans to act as nitrogen oxide sources in a living organism,[1,2] and, hence, with the possibility of developing diverse medicines based on these compounds. It has been found[3] that the metabolism of these derivatives in an organism involves S-containing enzyme systems. Only few examples of substitution of S-containing nucleophiles in the furoxan series can be found in the literature; in addition, these reactions have been carried out only for functional groups attached directly to a furoxan ring (for example, NO_2 [4,5] and Cl [6]). No examples in which groups not bound directly to the heterocyclic nucleus are replaced by nucleophiles have been reported. In this study, we attempted to carry out the replacement of a Br atom in bromoacetyl derivatives of furoxan and furazan by S-containing nucleophiles. Previously, we have described a convenient preparative procedure for the synthesis of these compounds.[7]

When our study mentioned above[7] had already been published, a method for the preparation of previously inaccessible 3-acetyl-4-aminofuroxan (**1a**) and 3-acetyl-4-nitrofuroxan[8] (**1b**) has been reported; therefore, we extended the series of furoxan bromoacetyl derivatives by synthesizing 4-amino-3-bromoacetylfuroxan (**2a**) and 3-bromoacetyl-4-nitrofuroxan (**2b**). The bromoacetyl derivative **2a** was prepared in a nearly quantitative yield by treatment of a suspension of the starting compound **1a** in concentrated HCl with an equimolar amount of Br_2. The bromoacetyl derivative of nitrofuroxan **2b** was obtained by two methods: by oxidation of the amino group in the amino derivative **2a** with trifluoroperoxyacetic acid and by bromination of compound **1b** under the conditions used to prepare **2a** (Scheme 1). Nitro derivative **2b** proved to be relatively unstable; therefore, we did not use it in this study.

Scheme 1



As S-nucleophiles, we chose thiourea and various heterocyclic thiols. It is known that haloacetyl derivatives react with thiourea to give the corresponding isothiuronium salts, which then undergo Hanzsch cyclization to yield 2-aminothiazole. We found that bromoacetyl derivatives of furoxan behave in a similar way: they also react with thiourea in acetone at room temperature to give aminothiazole derivatives, and the outcome of the reaction does not depend on the position of the *N*-oxide O atom with respect to the bromoacetyl fragment in the initial furoxan (Scheme 2). In the case of furoxan bis(bromoacetyl) derivative **2d** and its furazan analog **2e**, bis(aminothiazolyl)-substituted products were isolated. In both cases, the reaction apparently involves the intermediate formation of isothiuronium salts **3**, which spontaneously cyclize under the reaction conditions to afford 2-aminothiazole derivatives **4a**, **4c**, **4d**, and **4e**.

The reactions of furoxan and furazan bromoacetyl derivatives with heterocyclic thiols **5** occur less smoothly. The yields of products resulting from replacement of the Br atom by a sulfur-containing residue depends appreciably on the solvent used for the reaction. DMSO,

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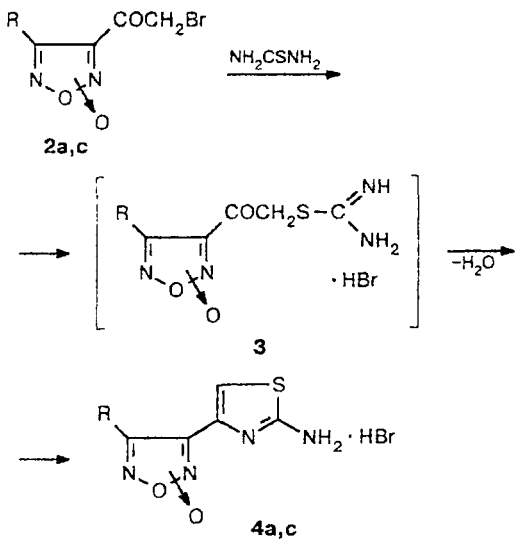
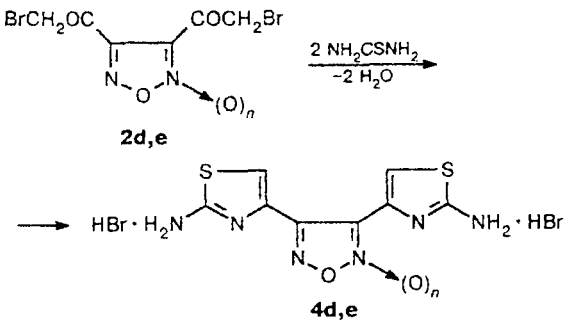
Scheme 2



R = 4-NH_2 (**2a**, **4a**); 3-Me (**2c**, **4c**)



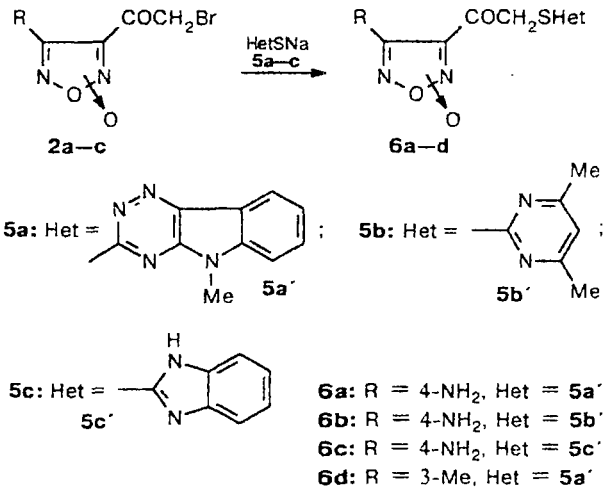
n = 1 (**2d**, **4d**); 0 (**2e**, **4e**)

DMF, and acetone were used as solvents. Only monobromoacetyl derivatives of furoxan and furazan could be introduced into this reaction. When bis(bromoacetyl) derivatives of furoxan **2d** and furazan **2e** were made to react with 9-methyl-1,3,4-triazacarbazole-2-thiol (**5a**) and benzimidazole-2-thiol (**5c**) in acetone, DMSO, or DMF, the reaction mixture completely resinified without formation (according to TLC) of any individual compounds.

The substrates reacted with the sodium salts of thiols, which formed directly in the reaction mixture when excess $NaHCO_3$ was added to a suspension of the corresponding thiol. The best yields were attained at room temperature, and acetone proved to be the best solvent for this reaction.

For example, the reactions of 4-amino-3-bromoacetylfuroxan **2a** with 9-methyl-1,3,4-triazacarbazole-2-thiol (**5a**) in DMF and with 4,6-dimethylpyrimidine-2-thiol (**5b**) and benzimidazole-2-thiol (**5c**) in acetone gave the corresponding 4-amino-3-(hetarylthioacetyl)furoxans (**6a—c**) in fairly good yields. It is noteworthy that

Scheme 3



the reaction of compound **2a** with thiol **5c** in DMF afforded no nucleophilic substitution product **6c**; instead, resinification of the reaction mixture occured.

Substitution product **6d** was obtained from 4-bromoacetyl-3-methylfuroxan **2c** and thiol **5a** both in acetone and in DMF; a higher yield of the product was achieved in the former case (Scheme 3).

Furazan derivatives containing one bromoacetyl substituent react with thiols similarly to furoxan derivatives. The reactions of 3-bromoacetyl-4-methylfurazan (**2f**) with thiol **5b** in acetone and of 3-amino-4-bromoacetyl-

Scheme 4

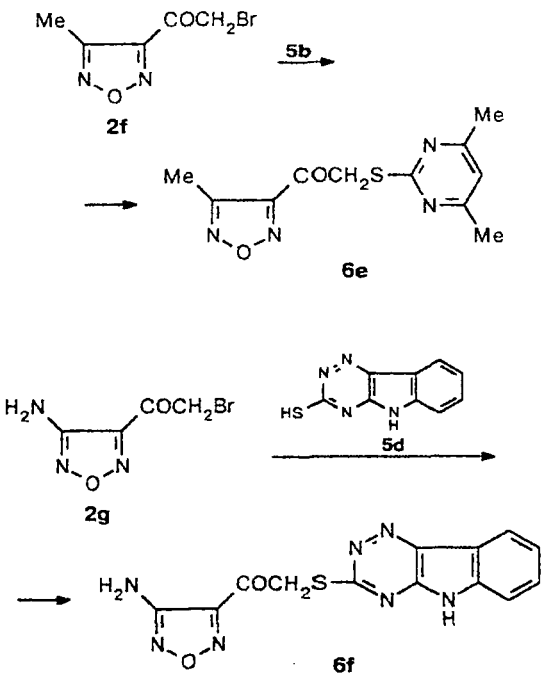


Table 1. Yields and some physicochemical characteristics of the synthesized furoxans and furazans

Compound	Yield (%)	M.p./°C	R_f (eluent)	Found / Calculated (%)			Molecular formula
				C	H	N	
2a	97	179—180	0.37 ($CHCl_3$)	23.22 23.46	1.93 1.81	19.04 18.93	$C_4H_4BrN_3O_3$
2b	38 (*A*) 48 (*B*)	—[a]	0.62 ($CHCl_3$)	—	—	—	$C_4H_2BrN_3O_5$
4a	55	160—170 (decomp.)	—	21.61 21.43	2.28 2.14	24.83 25.02	$C_5H_6BrN_5O_2S$
4c	61	160—170 (decomp.)	—	26.05 25.81	2.80 2.51	21.98 20.07	$C_6H_7BrN_4O_2S$
4d	60	230—240 (decomp.)	—	21.44 21.62	1.90 1.80	18.98 18.92	$C_8H_8Br_2N_6O_2S_2$
4e	44	240—250 (decomp.)	—	22.17 22.43	1.98 1.87	20.02 19.63	$C_8H_8Br_2N_6OS_2$
6a	74[b]	201—202	0.38 (C_6H_6—AcOEt, 3 : 1)	46.35 47.06	3.30 3.08	27.98 27.45	$C_{14}H_{11}N_7O_3S$
6b	62[c]	133—134	0.48 (C_6H_6—AcOEt, 3 : 1)	42.47 42.71	3.90 3.92	24.98 24.91	$C_{10}H_{11}N_5O_3S$
6c	71[c]	160—161	0.44 (C_6H_6—AcOEt, 3 : 1)	45.75 45.36	3.20 3.09	23.98 24.06	$C_{11}H_9N_5O_3S$
6d	82[c]	199—200	0.68 (C_6H_6—AcOEt, 3 : 1)	50.39 50.56	3.52 3.37	23.28 23.61	$C_{15}H_{12}N_6O_3S$
6e	73[c]	67—69	0.46 (C_6H_6—AcOEt, 3 : 1)	50.47 50.02	4.26 4.56	20.98 21.22	$C_{11}H_{12}N_4O_2S$
6f	74[d]	243—245	0.39 (C_6H_6—AcOEt, 3 : 1)	50.82 50.46	2.90 2.76	30.30 29.98	$C_{13}H_9N_7O_2S$

[a] Oil. [b] The reaction was carried out in DMF. [c] In acetone. [d] In DMSO.

furazan (**2g**) with thiol **5d** in DMSO made it possible to synthesize hetarylthioacetylfurazan derivatives **6e** and **6f** in preparative yields (Scheme 4).

Experimental

IR spectra were recorded on a UR-20 spectrometer for KBr pellets. ^1H, ^{13}C, and ^{14}N NMR spectra were measured on a Bruker AM-300 instrument (300, 75.5, and 21.5 MHz, respectively). The chemical shifts were referred to internal $SiMe_4$ (for ^1H and ^{13}C NMR) or external $MeNO_2$ standard (for ^{14}N NMR). The mass spectrum was recorded on a Finnigan MAT INCOS-50 instrument (EI, 70 eV). TLC was carried out on Silufol UV-254 plates; the plates were visualized by UV irradiation.

The main characteristics of the compounds synthesized are listed in Tables 1 and 2.

4-Amino-3-bromoacetylfuroxan (2a). Bromine (10 mmol) was added dropwise to a suspension of 4-amino-3-acetylfuroxan (**1a**) (10 mmol) in 20 mL of concentrated HCl. The reaction mixture was stirred for 24 h at ~20 °C and diluted with an equal volume of water. The precipitate was filtered off and dried in air to give virtually pure compound **2a**, whose properties did not change after recrystallization from $CHCl_3$. ^{14}N NMR (CD_3COCD_3), δ: −338.33 (NH_2, $\Delta\nu_{1/2}$ = 515 Hz).

3-Bromoacetyl-4-nitrofuroxan (2b). *A.* Bromination of 3-acetyl-4-nitrofuroxan (**1b**) was carried out as described above. After dilution of the reaction mixture with water, the product was extracted with CH_2Cl_2, washed with water, dried with $MgSO_4$, and concentrated on a rotary evaporator to give compound **2b** in 38% yield as a yellow oil that gradually decomposed at room temperature. Product **2b** could not be isolated in an analytically pure state. ^{14}N NMR (CD_3COCD_3), δ: −37.82 (NO_2, $\Delta\nu_{1/2}$ = 14.5 Hz).

B. Oxidation of 4-amino-3-bromoacetylfuroxan (**2a**). At 15 °C, 4-amino-3-bromoacetylfuroxan (**2a**) (10 mmol) was added in one portion to a mixture of 50 mL of CH_2Cl_2, 10 mL of trifluoroacetic anhydride, and 1.25 mL of 90% H_2O_2. The reaction mixture was stirred at ~20 °C until the precipitate dissolved (4—5 h), kept for 12 h at ~20 °C, and poured into 40 mL of water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL).

The combined extracts were washed with water (2×15 mL), dried with $MgSO_4$, and concentrated to give compound **2b** in 48% yield as a yellow oil identical to the sample prepared by procedure *A*.

Table 2. ^1H and ^{13}C NMR and IR spectra of the compounds synthesized

Compound	Solvent	^1H NMR, δ	^{13}C NMR, δ	IR, ν/cm^{-1}
2a	CD_3COCD_3	4.48 (s, 2 H, CH_2); 6.21 (s, 2 H, NH_2)	34.2 (CH_2); 109.6 (C—CO); 157.6 (C—NH_2); 183.5 (CO)	680, 720, 740, 960, 1025, 1110, 1195, 1250, 1350, 1380, 1510, 1595, 1625, 1690, 2250, 2995, 3340, 3450
2b	CD_3COCD_3	4.37 (s, 2 H, CH_2)	46.3 (CH_2); 106.1 (C—CO); 155.9(C—NO_2); 177.3 (CO)	700, 790, 985, 1310, 1400, 1580, 1700, 3250
4a	CD_3SOCD_3	5.85 (br.s, 2 NH_2, H_2O); 7.45 (s, 1 H, CH arom.)	105.6 (C(3) of the furoxan ring); 108.2 (C(5) of the thiazole ring); 133.9 (C(4) of the thiazole ring); 156.0 (C(4) of the furoxan ring); 169.3 (C(2) of the thiazole ring)	760, 835, 865, 900, 1000, 1070, 1180, 1260, 1320, 1460, 1550, 1640, 1700, 2930, 3350 br
4c	CD_3SOCD_3	2.33 (s, 3 H, CH_3); 7.30 (br.s, 2 NH_2, H_2O); 7.32 (s, 1 H, CH arom.)	9.9 (CH_3); 110.6 (C(3) of the furoxan ring); 113.5 (C(5) of the thiazole ring); 138.0 (C(4) of the thiazole ring); 153.5 (C(4) of the furoxan ring); 170.1 (C(2) of the thiazole ring)	760, 835, 865, 900, 1000, 1070, 1180, 1260, 1320, 1460, 1550, 1640, 1700, 2930, 3350
4d	CD_3SOCD_3	7.50 (br.s, 2 NH_2, H_2O); 7.74 (s, 1 H, CH); 8.02 (s, 1 H, CH arom.)	109.7 (C(3) of the furoxan ring); 111.4, 112.6 (C(5) of the thiazole ring); 128.0, 129.7 (C(4) of the thiazole ring); 147.7 (C(4) of the furoxan ring); 169.1, 169.6 (C(2) of the thiazole ring)	710, 755, 790, 910, 1035, 1090, 1280, 1360, 1440, 1660, 3250 br
4e	CD_3SOCD_3	6.60 (br.s, 2 NH_2, H_2O); 7.78 (s, 2 H, 2 CH arom.)	112.3 (C(5) of the thiazole ring); 129.9 (C(4) of the thiazole ring); 146.3 (C of the furazan ring); 169.6 (C(2) of the thiazole ring)	720, 750, 845, 910, 940, 970, 1020, 1085, 1115, 1210, 1270, 1430, 1580, 1660, 3250 br
6a	CD_3SOCD_3	3.72 (s, 3 H, CH_3); 4.82 (s, 2 H, CH_2); 6.51 (s, 2 H, NH_2); 7.40—8.30 (m, 4 H, CH arom.)	26.9 (CH_3); 38.30 (CH_2); 109.2 (C(3) of the furoxan ring); 156.3 (C(4) of the furoxan ring); 185.0 (CO); 110.8, 117.0, 121.2, 122.7, 130.8, 140.9, 141.4, 145.8, 165.3 (heterocyclic C in **5a**)	735, 755, 805, 860, 885, 970, 1010, 1090, 1185, 1280, 1330, 1360, 1470, 1490, 1585, 1630, 1700, 2930, 3160, 3240
6b	CD_3SOCD_3	2.24 (s, 6 H, 2 CH_3); 4.52 (s, 2 H, CH_2); 6.58 (s, 2 H, NH_2); 6.96 (s, 1 H, CH arom.)	23.0 (CH_3); 37.2 (CH_2); 109.5 (C(3) of the furoxan ring); 116.2 (C(5) of the pyrimidine ring); 156.4 (C(4) of the furoxan ring); 167.1 (C(4) of the pyrimidine ring); 168.3 (C(2) of the pyrimidine ring); 186.1 (CO)	730, 760, 845, 865, 895, 960, 1190, 1250, 1265, 1280, 1345, 1370, 1450, 1505, 1585, 1630, 1685, 3350, 3460
6c	CD_3SOCD_3	4.80 (s, 2 H, CH_2); 6.65 (s, 2 H, NH_2); 7.15 (m, 2 H, CH arom.); 7.45 (m, 2 H, CH arom.); 10.55 + 12.50 (1 H, NH)	40.1 (CH_2); 108.4 (C(3) of the furoxan ring); 148.4 (C(2) of the imidazole ring); 156.4 (C(4) of the furoxan ring); 184.4 (CO); 109.3, 109.4, 120.4, 122.2, 121.5 (C of the benzene ring)	750, 855, 885, 970, 1015, 1040, 1200, 1240, 1275, 1370, 1450, 1515, 1630, 1680, 3330, 3480
6d	CD_3SOCD_3	2.28 (s, 3 H, C—CH_3); 3.70 (s, 3 H, N—CH_3); 4.92 (s, 2 H, CH_2); 6.51 (s) + 7.45—8.35 (m) (4 H, CH arom.)	—*	760, 805, 860, 875, 955, 980, 1060, 1085, 1185, 1270, 1330, 1360, 1470, 1580, 1635, 1730, 2950
6e	CD_3SOCD_3	2.18 (s, 9 H, 3 CH_3); 4.70 (s, 2 H, CH_2); 6.92 (s, 1 H, CH arom.)	8.7 (CH_3—C of the furazan ring); 23.0 (CH_3 of the pyrimidine ring); 38.7 (CH_2); 116.1 (C(5) of the pyrimidine ring); 156.4 (C of the furazan ring); 167.0 (C(4) of the pyrimidine ring); 168.3 (C(5) of the pyrimidine ring); 187.6 (CO)	730, 885, 915, 995, 1040, 1275, 1350, 1375, 1440, 1470, 1545, 1690, 1715

(to be continued)

Table 2 (*continued*)

Compound	Solvent	^{1}H NMR, δ	^{13}C NMR, δ	IR, ν/cm^{-1}
6f	CD_3SOCD_3	4.95 (s, 2 H, CH_2); 6.45 (s, 2 H, NH_2); 7.30—8.45 (m, 4 H, 4 CH arom.); 12.55 (s, 1 H, NH)	38.9 (CH_2); 146.4 (C—CO of the furazan ring); 155.8 (C—NH_2 of the furazan ring); 187.7 (CO); 112.8, 117.5, 121.6, 122.6, 131.1, 140.4, 141.2, 143.3, 165.5 (heterocyclic C in **5d**)	720, 750, 780, 860, 890, 995, 1095, 1200, 1220, 1275, 1350, 1380, 1435, 1460, 1625, 1710, 3000

* For compound **6d**, the ^{13}C NMR spectrum could not be recorded due to its poor solubility in organic solvents. This product was characterized by mass spectrometry. MS, *m/z* (I_{rel} (%)): 356 [M^+] (1), 340 [M^+—O] (11), 326 [M^+—NO] (62), 296 [M^+—2NO] (15), 257 [M^+—methylfuroxanyl] (62), 229 [M^+—methylfuroxanoyl] (100), 215 [M^+—methylfuroxanoylmethyl] (19), 201 (40), 187 (43), 171 (9), 160 (12), 155 (15), 143 [methylfuroxanoylmethyl—NO] (98), 128 [methylfuroxanoyl].

2-Aminothiazol-4-ylfuroxan and -furazan hydrobromides 4a,c—e (general procedure). At ~20 °C, furoxan bromoacetyl derivative **2a** or **2c** (5.5 mmol) was added in several portions to a stirred solution of thiourea (0.38 g, 5 mmol) in 25 mL of acetone. In the case of bis(bromoacetyl) derivatives **2d,e**, the corresponding furoxan or furazan (5 mmol) was added to a solution of thiourea (11.5 mmol) in 40 mL of acetone. After some period, formation of a precipitate began. The reaction mixture was stirred for 48 h, and the precipitate was filtered off, washed on the filter with 3 mL of ice water and 10 mL of acetone, and dried in air. The products decomposed without melting.

Hetarylthioacetylfuroxans or -furazans 6a—f (general procedure). $NaHCO_3$ (7.5 mmol) was added to a suspension of a thiol (5 mmol) in 20 mL of an organic solvent (in the case of compound **5b**, the corresponding hydrochloride was used, and an additional quantity of $NaHCO_3$ needed to neutralize HCl was added). The mixture was stirred for 30 min, and a furoxan or furazan bromoacetyl derivative (5 mmol) was added. The reaction mixture was stirred for 8 h (synthesis of **6a,d,f**) or for 48 h (synthesis of **6b,c,e**), 100 mL of water was added, and the resulting precipitate was filtered off. The product was washed on the filter with water, with a solution of Na_2CO_3, again with water, with a small amount of ethanol (except for compounds **6b,e**), and with ether and dried in air.

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