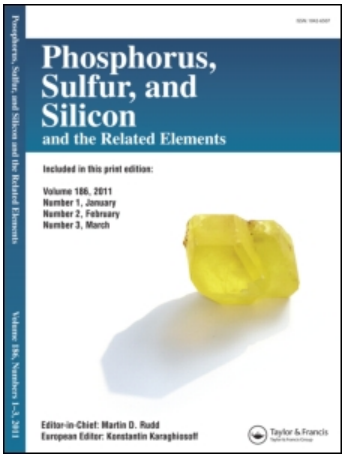

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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Online publication date: 27 October 2010

To cite this Article Yarovenko, V. N. , Es'kov, A. A. , Zavarzin, I. V. , Chernoburova, E. I. , Martynkin, A. Yu. and Krayuskin, M. M.(2003) 'Synthesis of Carbamoyl-Containing N,S-Heterocyclic Compounds', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 6, 1283 — 1288

To link to this Article: DOI: 10.1080/10426500307911

URL: http://dx.doi.org/10.1080/10426500307911

Phosphorus, Sulfur, and Silicon, 178:1283–1288, 2003

ISSN: 1042-6507 print
DOI: 10.1080/10426500390200576

SYNTHESIS OF CARBAMOYL-CONTAINING N,S-HETEROCYCLIC COMPOUNDS

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(Received October 24, 2002; accepted November 22, 2002)

Monothioxamides unsubstituted at the thioamidic nitrogen atom were obtained by the reaction of NS-morpholino-NO-R-thioxamides with ammonia. Carbamoyl-containing 5-phenylcarbamoyl-1,2,4-dithiazoles, 6-phenylcarbamoyl-5,6-dihydro-[1,2,4,5]-dithiadiazin-3-one, and 5-phenylcarbamoyl-2-oxy-1,3,4-thiadiazole were synthesized by the reaction of monothioxamides or thiohydrazides of oxamic acids with chlorocarbonylsulfenyl chloride.

Keywords: Chlorocarbonylsulfenyl chloride; 5,6-dihydro-1,2,4,5-dithiadiazin-3-one; 1,2,4-dithiazoles; 2-hydroxy-1,3,4-thiadiazole; monothioxamides; thiohydrazides of oxamic acids

Monothioxamides and thiohydrazides of oxamic acids having in one molecule the thioamide or thiohydrazide as well as an amide moiety are convenient starting reagents in the synthesis of various compounds.[1–3]

We previously have developed a convenient simple method for the synthesis of NS-monosubstituted and disubstituted monothioxamides, which consists of the interaction of a solution of elementary sulfur in amines with available α-chloracetamides at room temperature.[4] We also showed that NS-morpholino-NO-R-thioxamides are smoothly transformed into thiohydrazides of oxamic acids by hydrazine.[5]

In continuation of our work on the use of products of the S-functionalization of organic compounds in the synthesis of S,N-heterocyclic compounds,[4–10] we studied the reaction of monothioxamides and thiohydrazides of oxamic acids with chlorocarbonylsulfenyl chloride.

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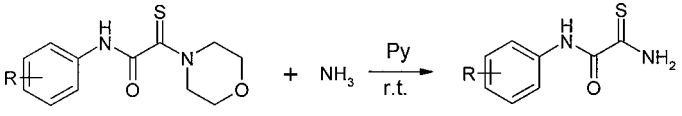
Monothioxamides unsubstituted at the thioamidic nitrogen atom (**2a–e**) were synthesized by the reaction of N^S-morpholino-N^O-R-thioxamides with ammonia (Scheme 1). Transamination occurs under mild conditions at room temperature in a high yield.

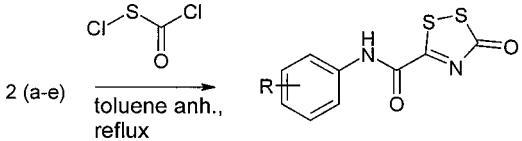


1(a-e) 2(a-e)

2a, R = 4-F;
2b, R = 2,6-Me;
2c, R = 4-CH_3CONH;
2d, R = 3-OCH_3;
2e, R = 3-CH_3;

SCHEME 1

The reaction of monothioxamides **2a–e** with chlorocarbonylsulfenyl chloride on heating in toluene (Scheme 2) afforded carbamoyl-containing 3-oxo-3H-1,2,4-dithiazoles (**3a–e**).

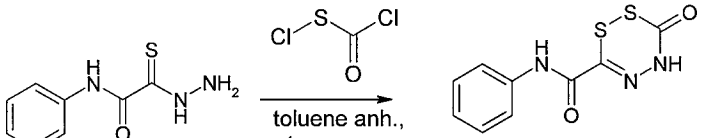


3(a-e)

3a, R = 4-F;
3b, R = 2,6-Me;
3c, R = 4-CH_3CONH;
3d, R = 3-OCH_3;
3e, R = 3-CH_3;

SCHEME 2

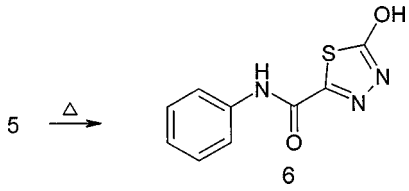
The reaction of thiohydrazide of oxamic acid (**4**) with chlorocarbonylsulfenyl chloride at room temperature (Scheme 3) produced the corresponding 6-phenylcarbamoyl-5,6-dihydro-[1,2,4,5]dithiadiazin-3-one (**5**).



4 5

SCHEME 3

Heating of compound **5** (Scheme 4) resulted in the elimination of the sulfur atom and formation of 5-phenylcarbamoyl-2-oxy-1,3,4-thiadiazole (**6**). The substance also can be obtained on heating a mixture of thiohydrazides of **4** with chlorocarbonylsulfenyl chloride.



SCHEME 4

Derivatives of 2-hydroxy-1,3,4-thiadiazoles can be of interest as biologically active compounds.[11,12] The hydroxy group in 1,3,4-thiadiazoles is used for the introduction of various substituents into the 2-position of the cycle.[13,14]

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker WM-200 (200 MHz) and Bruker WM-250 (250 MHz) instruments in DMSO-d_6 relative to HMDS. Mass spectra were obtained on a Varian MAT CH-6 instrument with the direct injection of a sample into the ion source, an ionization energy of 70 eV, and an accelerating voltage of 1.75 kV. Melting points were measured on a Boetius heating stage. All reactions mixtures were analyzed and purity of isolated products was monitored by TLC on Silufol UV-254 plates in the EtAc-hexane (1:1, vol/vol) system.

Phenylthioxacetamides 2(a–e)

General Procedure

Anhydrous ammonia was passed through a solution of monothioxamide (0.05 mmol) in pyridine (10 ml) until the initial substances disappeared (TLC monitoring). Then the mixture was poured into water (100 ml). The precipitate that formed was filtered off, washed with water, dried, and recrystallized from ethanol.

1-N-(4-Fluorophenyl)-2-amino-2-thioxacetamide (2a): 70% yield, m.p. 146–147°C. ^{1}H NMR (DMSO-d_6) ppm: 7.20 (d, 2H, phenyl proton), 7.75 (d, 2H, phenyl proton), 10.00 (s, 2H, NH_2), 10.35 (s, 1H, NH). Mass; *m/z*: 198 (M^+). Anal. Calcd. for $C_8H_7FN_2OS$: C,

48.47; H, 3.56; N, 14.13; S, 16.18. Found: C, 48.54; H, 3.51; N, 14.11; S, 16.21.

1-N-(2,6-Dimethylphenyl)-2-amino-2-thioxacetamide (2b): 73% yield, m.p. 177–178°C. ^{1}H NMR (DMSO-d_6) ppm: 2.20 (s, 6H, CH_3); 7.10 (br.m, 3H, phenyl proton), 9.85 (s, 2H, NH), 10.35 (s, 1H, NH). Mass, *m/z*: 208 (M^+). Anal. Calcd. for $C_{10}H_{12}N_2OS$: C 57.67, H 5.81, N 13.45, S 15.40. Found: C 57.70, H 5.75, N 13.42, S 15.43.

1-N-(4-Acetaminophenyl)-2-amino-2-thioxacetamide (2c): 72% yield, m.p. 256–257°C. ^{1}H NMR (DMSO-d_6) ppm: 2.05 (s, 3H, CH_3); 7.55 (d, 2H, phenyl proton); 7.65 (d, 2H, phenyl proton); 9.85 (c, 1H, NH); 10.10 (c, 2H, NH_2); 10.25 (c, 1H, NH). Mass, *m/z*: 237 (M^+). Anal. Calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71; S, 13.51. Found: C, 50.66; H, 4.64; N, 17.69; S, 13.53.

1-N-(3-Methoxyphenyl)-2-amino-2-thioxacetamide (2d): 68% yield, m.p. 143–144°C. ^{1}H NMR (DMSO-d_6) ppm: 3.75 (c, 3H, CH_3); 6.70 (br.m, 1H, phenyl proton); 7.30 (br.m, 2H, phenyl proton); 7.40 (s, 1H, phenyl proton); 10.00 (s, 2H, NH_2); 10.25 (s, 1H, NH). Mass, *m/z*: 210 (M^+). Anal. Calcd. for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32; S, 15.25. Found: C, 51.45; H, 4.76; N, 13.29; S, 15.28.

1-N-(3-Tolyl)-2-amino-2-thioxacetamide (2e): 66% yield, m.p. 157–158°C. ^{1}H NMR (DMSO-d_6) ppm: 3.25 (s, 3H, CH_3); 6.95 (π, 1H, phenyl proton); 7.25 (t, 1H, Ar, phenyl proton); 7.55 (d, 1H, phenyl proton); 7.63 (s, 1H, phenyl proton); 9.55 (s, 1H, NH); 10.25 (s, 1H, NH); 10.40 (s, 1H, NH). Mass, *m/z*: 194 (M^+). Found: C, 55.69; H, 5.15; N, 14.39; S, 16.55. Anal. Calcd. for $C_9H_{10}N_2OS$: C, 55.65; H, 5.19; N, 14.42; S, 16.51.

5-Phenylcarbamoyl-1,2,4-dithiazol-3-ones (3a–e)

General Procedure

Chlorocarbonylsulfenyl chloride (0.06 mmol) was added to a solution of phenylaminothioxacetamide **2** (0.05 mmol) in anhydrous toluene (15 ml), and the mixture was stirred for 30 min. Then the reaction mixture was refluxed for 1–2 h until the initial substance disappeared (TLC monitoring). The precipitate that formed on cooling was filtered off and recrystallized from ethanol.

5-N-(4-Fluorophenyl)carbamoyl-1,2,4-dithiazol-3-one (3a): 83% yield, m.p. 191–193°C. ^{1}H NMR (DMSO-d_6) ppm: 6.90 (d, 2H, phenyl proton); 7.70 (d, 2H, phenyl proton); 10.60 (s, 1H, NH). Mass, *m/z*: 256 (M^+). Anal. Calcd. for $C_9H_5FN_2O_2S_2$: C, 42.18; H, 1.97; N, 10.93; S, 25.02. Found: C, 42.25; H, 2.03; N, 10.85; S, 24.96.

5-N-(2,6-Dimethylphenyl)carbamoyl-1,2,4-dithiazol-one (3b): 85% yield, m.p. 166–168°C. ^{1}H NMR (DMSO-d_6) ppm: 2.25 (s, 6H, CH_3);

7.15 (br.m, 3H, phenyl proton); 8.25 (s, 1H, NH). Mass, *m/z*: 266 (M^+). Anal. Calcd. for $C_{11}H_{10}N_2O_2S_2$: C, 49.60; H, 3.78; N, 10.52; S, 24.08. Found: C, 49.65; H, 3.72; N, 10.49; S, 24.14.

5-N-(4-Acetanilide)carbamoyl-1,2,4-dithiazol-3-one (3c): 87% yield, m.p. 283–284°C. ^{1}H NMR (DMSO-d_6) ppm: 2.00 (br.m, 3H, CH_3); 7.55 (d, 2H, phenyl proton); 7.75 (d, 2H, phenyl proton); 9.80 (s, 1H, NH); 11.15 (s, 1 H, NH). Mass, *m/z*: 295 (M^+). Anal. Calcd. for $C_{11}H_9N_3O_3S_2$: C, 44.73; H, 3.07; N, 14.23; S, 21.71. Found: C, 44.76; H, 3.02; N, 14.25; S, 21.76.

5-N-(3-Methoxyphenyl)carbamoyl-1,2,4-dithiazol-3-one (3d): 84% yield, m.p. 172–175°C. ^{1}H NMR (DMSO-d_6) ppm: 3.85 (s, 3H, CH_3); 6.80 (d, 1H, phenyl proton); 7.15 (t, 1H, phenyl proton); 7.30 (d, 1H, phenyl proton); 7.40 (s, 1H, phenyl proton); 9.00 (s, 1H, NH). Mass, *m/z*: 268 (M^+). Anal. Calcd. for $C_{10}H_8N_2O_3S_2$: C, 44.76; H, 3.01; N, 10.44; S, 23.90. Found: C, 44.82; H, 2.97; N, 10.41; S, 23.96.

5-N-(3-Methylphenyl)carbamoyl-1,2,4-dithiazol-3-one (3e): 83% yield, m.p. 158–160°C. ^{1}H NMR (DMSO-d_6) ppm: 2.40 (s, 3H, CH_3); 7.05 (d, 1H, phenyl proton); 7.30 (t, 2H, phenyl proton); 7.58 (d, 1H, phenyl proton); 7.66 (s, 1H, phenyl proton); 9.00 (s, 1H, NH). Mass, *m/z*: 252 (M^+). Anal. Calcd. for $C_{10}H_8N_2O_2S_2$: C, 47.60; H, 3.20; N, 11.10; S, 25.42. Found: C, 47.66; H, 3.16; N, 11.07; S, 25.47.

Synthesis of 6-Phenylcarbamoyl-5,6-dihydro-[1,2,4,5]dithiadiazin-3-one (5)

Chlorocarbonylsulfenyl chloride (0.1 mmol) was added to a solution of thiohydrazide (**4**) (0.05 mmol) in anhydrous toluene (15 ml), and the mixture was stirred for 6 h at room temperature. The solvent was removed in vacuo. The reaction product was isolated from the reaction mixture using flash chromatography (silica gel, methylene dichloride-light petroleum (1:1) as eluent). The yield was 60%, m.p. 166–168°C. ^{1}H NMR (DMSO-d_6) ppm: 7.35 (br.m, 3H; phenyl proton); 7.75 (d, 2H, phenyl proton); 10.55 (s, 1H, NH) 12.10 (s, 1H, NH). Mass, *m/z*: 253 (M^+). Anal. Calcd. for $C_9H_7N_3O_2S_2$: C, 42.67; H, 2.79; N, 16.59; S 25.32. Found: C, 42.72; H, 2.74; N, 16.54; S, 25.38.

Synthesis of 5-Phenylcarbamoyl-2-oxy-1,3,4-thiadiazole (6)

Chlorocarbonylsulfenyl chloride (0.1 mmol) was added to a solution of thiohydrazide (**4**) (0.05 mmol) in anhydrous toluene (15 ml), and the mixture was boiled for 4 h. Then the solvent was removed in vacuo. The reaction product was isolated from the reaction mixture by flash

chromatography (silica gel, methylene dichloride-light petroleum (1:1) as eluent). The yield was 75%, m.p. 185–186°C. ^{1}H NMR (DMSO-d_6) ppm: 3.95 (s, 1H, H); 7.35 (br.m, 1H, phenyl proton); 7.75 (br.m, 1H, phenyl proton); 7.85 (br.m, 1H, phenyl proton); 11.15 (s, 1H, NH). Mass, *m/z*: 221 (M^+). Anal. Calcd. for $C_9H_7N_3O_2S$: C, 48.86; H, 3.19; N, 18.99; S 14.49. Found: C, 48.92; H, 3.15; N, 18.96; S, 14.54.

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