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Synthesis and Reactions of 2-Mercaptomethyl-1,3,4-oxadiazolin-5-one

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Summary. The title compound (**4**) was synthesized from thioglycolic acid hydrazide and ethyl chloroformate. The reactions of **4** with aromatic amines, amino derivatives, hydrazine hydrate, hydroxylamine, and formamide were studied. Addition of compound **4** to α,β-unsaturated compounds, *i.e.* chalcones, maleic anhydride, quinones, and acrylonitrile, was investigated.

Keywords. 1,3,4-Oxadiazole; Nitrogen nucleophiles; Cycloaddition.

Synthese und Reaktionen von 2-Mercaptomethyl-1,3,4-oxadiazolin-5-on

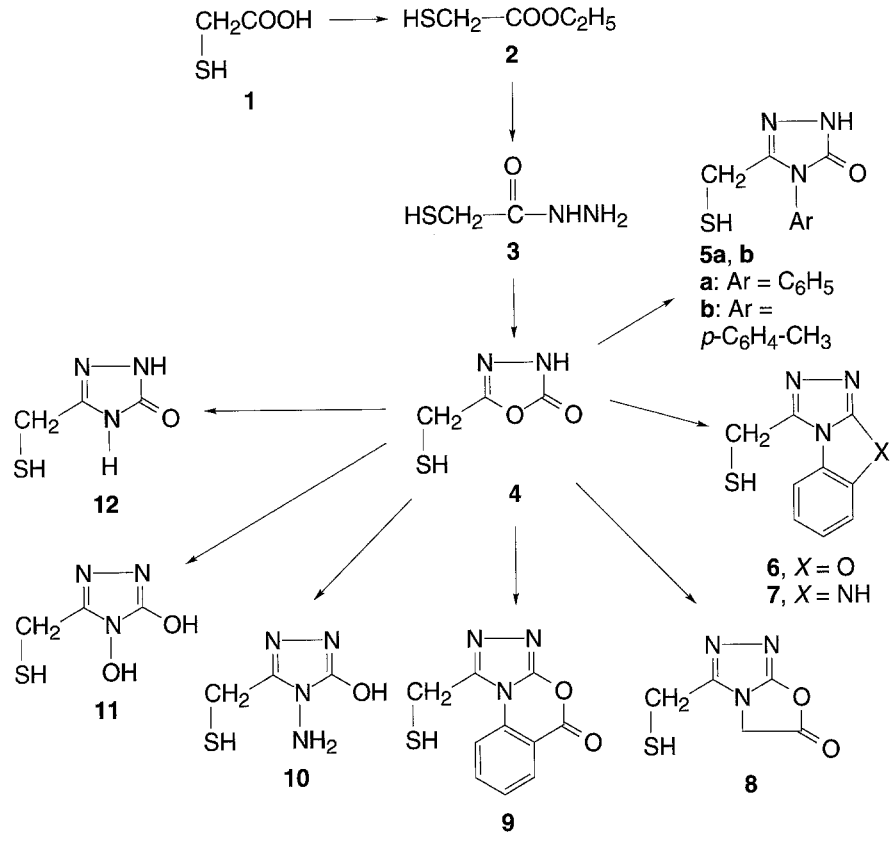
Zusammenfassung. Die Titelverbindung (**4**) wurde aus Thioglycolsäurehydrazid und Chlorameisensäureethylester hergestellt. Die Reaktionen von **4** mit aromatischen Aminen, Aminoderivaten, Hydrazinhydrat, Hydroxylamin und Formamid sowie die Addition von **4** an α,β-ungesättigte Verbindungen (Chalkone, Maleinsäureanhydrid, Chinone, Acetonitril) wurden untersucht.

Introduction

A number of 1,3,4-oxadiazole derivatives have been reported to exert most notable antimicrobial, muscle relaxent, and tranquilizing activities [1–3]. Moreover, several 1,3,4-oxadiazolones have fungicidal [4], herbicidal [5], and antitubercular [6] activities. In addition 1,2,4-triazole derivatives exhibit pronounced antibacterial [7], antifungial [8], analgesic, and antiinflammatory [9–11] activities. These observations prompted us to synthesize the oxadiazoles **4** and **13–19** as well as 1,2,4-triazole derivatives **5–12**.

Results and Discussion

The new compounds were prepared as shown in Schemes 1 and 2. The acid hydrazide **3** required as starting material, was prepared from the corresponding ester **2** according to Ref. [12, 13]. The oxadiazole derivative **4** was synthesized by refluxing **3** with ethyl chloroformate. The triazole derivatives **5a, b** were prepared *via* the reaction of **4** with aromatic amines (aniline and *p*-toluidine) in boiling isopropanol. Reaction of **4** with *o*-aminophenol, *o*-phenylene diamine, glycine, and anthranilic acid in boiling isopropanol or ethanolic piperidine [14] afforded the corresponding



Scheme 1

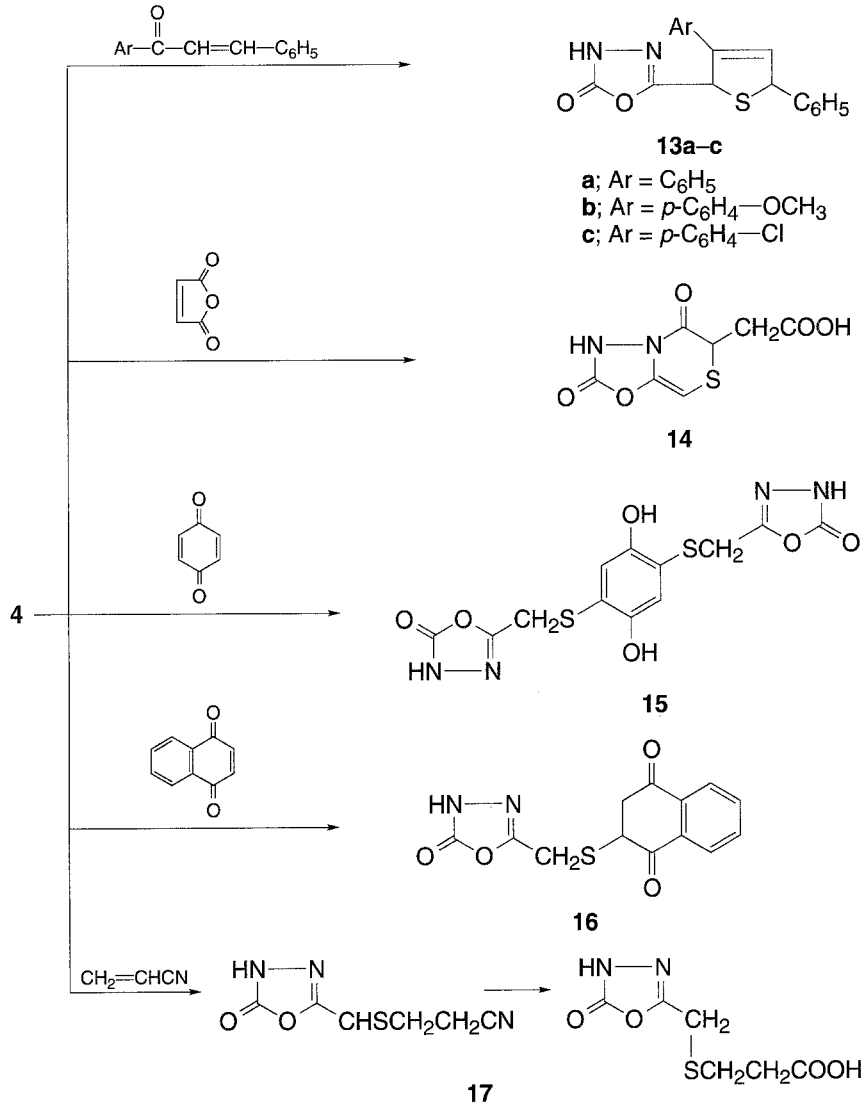
benzoxazole (**6**), benzimidazole (**7**), oxazole (**8**), and benzoxazinone (**9**) derivatives, respectively. Compound **10** was obtained by fusion of **4** with hydrazine hydrate [15] in an oil bath. On the other hand, compound **11** was prepared by treatment of **4** with hydroxylamine hydrochloride in boiling pyridine. Fusion of compound **4** with formamide in an oil bath at 180 °C affords the 1,2,4-triazolin-5-one derivative **12** [16] (Scheme 1).

Condensation or addition reactions of compound **4** with α,β-unsaturated compounds such as chalcones, maleic anhydride, 1,4-benzoquinone 1,4-naphthoquinone, and acrylonitrile provide the corresponding thiophene (**13a–c**), thiazine (**14**), quinol (**15**), naphthoquinone (**16**), and propionic acid (**17**) derivatives, respectively [17–20] (Scheme 2).

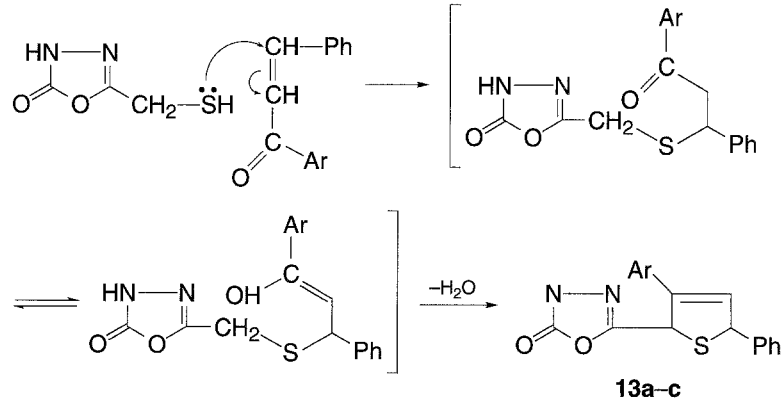
The formation of thiophene derivatives (**13a–c**) could be rationalized according to the reaction mechanism given in Scheme 3.

On the other hand cycloaddition of **4** to maleic anhydride may take place according to the following sequence (Scheme 4):

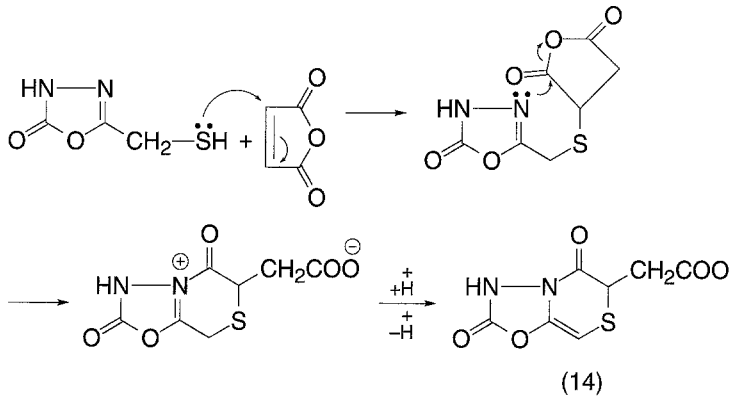
Compounds **4**, **6–9**, **12**, **15**, **16** and **17** were tested for antimicrobial activity using the agar diffusion method [21] against representatives of gram positive bacteria (*bacillus subtilis* and *staphylococcus aureus*) and gram negative bacteria (*E. coli* and *Pseudomones aeruginosa*). The result obtained are summarized in Table 1.



Scheme 2



Scheme 3



Scheme 4

Table 1. Antimicrobial activity of prepared compounds

	Gram positive		Gram negative	
	Bacillus subtilis	*Staphylococcus aureus*	*E. coli*	*Pseudomones aeruginosa*
4	+	+	−	−
6	−	++	−	+++
7	+	+++	−	++
8	++	+++	+	+
9	+++	+++	−	+++
12	++	−	−	+
15	++	+++	−	−
16	+	+	−	−
17	+++	+++	+++	+++

−: Not sensitive; +: slightly sensitive (inhibition zone 3–5 mm); ++: moderately sensitive (inhibition zone 5–10 mm); +++: fairly sensitive (inhibition zone 10–15 mm)

Experimental

Melting points: uncorrected; IR spectra: Pye-Unicam Sp1000 spectrophotometer; NMR spectra: Varian GEMINI 200.

2-Mercaptomethyl-1,3,4-oxadiazolin-5-one (**4**)

A mixture of thioglycolic acid hydrazide (**3** 0.01 mol) and ethyl chloroformate (0.01 mol) was refluxed in an oil bath at 120 °C for 4 h. The separated solid was crystallized from EtOH. Mp.: 115 °C; Yield: 75%; $C_3H_4N_2O_2S$ (132.1); calcd.: C 27.3, H 3.05, N 21.2; found: C 27.1, H 3.01, N 20.8; IR (KBr): $\nu = 3340$ (NH), 2650 (SH), 1680 (C=O), 1620 (C=N), 1120 (C–O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.99$ (s, 2 H, $-CH_2-$), 5.51 (br. s, 1 H, SH), 13.7(br. s, 1 H, (–NH–CO–) ppm.

3-Mercaptomethyl-4-phenyl- or -tolyl-1,2,4-triazolin-5-ones (**5a** and **5b**)

A mixture of **4** (0.01 mol) and the appropriate amine (aniline or *p*-toludine, 0.01 mol) in isopropanol was refluxed for 8 h. The separated solid was washed with isopropanol and crystallized.

5a: Mp.: 210 °C (EtOH); yield: 70%; $C_9H_9N_3OS$ (207.3); calcd.: C 52.2, H 4.37, N 20.3; found: C 51.8, H 4.23, N 20.1; IR (KBr): $\nu = 3360$ (NH), 2660 (SH), 1675 (C=O), 1610 (C=N) cm^{-1}.

5b: Mp.: 70 °C (EtOH); yield: 75%; $C_{10}H_{11}N_3OS$ (221.3); calcd.: C 54.3, H 5.01, N 18.1; found: C 54.1, H 4.98, N 17.7; ^1H NMR (*DMSO*-d_6): $\delta = 2.01$ (s, 3 H, $-CH_3$), 3.82 (s, 2 H, $-CH_2-$), 4.99 (br. s, 1 H, SH), 5.65–7.19 (m, 4 H, arom. protons), 13.21 (br. s, 1 H, –NH–CO–) ppm.

Benzoxazolo- or Benzimidazo[4,5-d]-3-mercaptomethyl-1,2,4-triazoles (**6**) *and* (**7**)

To a solution of **4** (0.01 mol) in isopropanol (50 ml), the *o*-aminophenol or *o*-phenylenediamine (0.01 mol) was added and the reaction mixture was refluxed for 8 h. The formed solid was washed with EtOH and crystallized.

6: Mp.: 85 °C (isopropanol); yield: 80%; $C_9H_7N_3OS$ (205.2); calcd.: C 52.7, H 3.44, N 20.5; found: C 52.4, H 3.19, N 20.1; IR (KBr): $\nu = 2700$ (SH), 1620 (C=N), 1130 (C–O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.86$ (s, 2 H, $-CH_2-$), 5.40 (br. s, 1 H, SH), 6.68–7.78 (m, 4 H, arom. protons) ppm.

7: Mp.: 140 °C (isopropanol); yield: 75%; $C_9H_8N_4S$ (204.3); calcd.: C 52.9, H 3.95, N 27.4; found: C 52.5, H 3.68, N 27.1; IR (KBr): $\nu = 3400$ (NH), 2600 (SH), 1590 (C=N) cm^{-1}.

Oxazolo-6-oxo[4,5-d]-3-mercaptomethyl-1,2,4-triazole (**8**)

A solution of **4** (0.01 mol) and glycine (0.01 mol) in alcoholic piperidine (50 ml) was refluxed for 10 h. The product obtained after concentration was crystallized from isopropanol. Mp.: 165 °C; yield: 85%; $C_5H_5N_3O_2S$ (170.3); calcd.: C 35.3, H 2.96, N 24.7; found: C 35.0, H 2.61, N 24.4; IR (KBr): $\nu = 2630$ (SH), 1700 (C=O), 1610 (C=N), 1100 (C–O) cm^{-1}.

3-Mercaptomethyl-1,2,4-triazolo[4,5-a]benzoxazin-9-one (**9**)

To a solution of **4** (0.01 mol) in isopropanol (50 ml), anthranilic acid (0.01 ml) was added and the reaction mixture was refluxed for 8 h. The separated solid was crystallized from isopropanol. Mp.: 130 °C; yield: 87%; $C_{10}H_7N_3O_2S$ (233.2); calcd.: C 51.5, H 3.03, N 18.0; found: C 51.1, H 2.81, N 17.6; IR (KBr): $\nu = 2650$ (SH), 1690 (C=O), 1605 (C=N), 1150 (C–O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.75$ (s, 2 H, $-CH_2$), 5.85 (br. s, 1 H, –SH), 6.67–7.73 (m, 4 H, arom. protons) ppm.

3-Mercaptomethyl-4-amino-5-hydroxy-1,2,4-triazole (**10**)

After refluxing **4** (0.01 mol) with hydrazine hydrate (0.015 mol) in an oil bath for 3 h, the separated solid was crystallized from acetic acid. Mp.: 80 °C; yield: 60%; $C_3H_6N_4OS$ (146.2); calcd.: C 24.7, H 4.14, N 38.3; found: C 24.5, H 3.73, N 37.9; IR (KBr): $\nu = 3340$ (NH), 2600 (SH), 1685 (C=O), 1590 (C=N) cm^{-1}.

3-Mercaptomethyl-4,5-dihydroxy-1,2,4-triazole (**11**)

A mixture of **4** (0.01 mol) and hydroxylamine hydrochloride in pyridine was refluxed for 6 h. On cooling, the mixture was poured into 100 ml dilute hydrochloric acid and the separated solid was crystallized from EtOH. Mp.: 110 °C; yield: 65%; $C_3H_5N_3O_2S$ (147.2); calcd.: C 24.5, H 3.43, N 28.6; found: C 24.1, H 3.19, N 28.3; IR (KBr): $\nu = 3400$ (NH or OH), 3650 (SH), 1690 (C=O), 1610 (C=N) cm^{-1}.

3-Mercaptomethyl-4H-1,2,4-triazolin-5-one (**12**)

Fusion of **4** (0.01 mol) with formamide (0.01 mol) in an oil both at 180 °C for 3 h afforded a solid which was crystallized from EtOH. Mp.: >300 °C; yield: 80%; $C_3H_5N_3OS$ (131.2); calcd.: C 27.5, H 3.84, N 32.0; found: C 27.4, H 3.61, N 31.8; IR (KBr): $\nu = 3340$ (NH or OH), 2630 (SH), 1700 (C=O), 1600 (C=N) cm^{-1}.

5-Oxo-4H-2-(3-(phenyl- or -p-methoxy phenyl- or -p-chlorophenyl)-5-phenyl-2,5-dihydrothiophen-2-yl)-1,3,4-oxadiazoline (**13a–c**)

A mixture of **4** (0.01 mol) and the appropriate chalcone (benzalacetophenone, benzal-*p*- methoxy-acetophenone, benzal-*p*-chloroacetophenone 0.01 mol was refluxed for 2 h in a methanol acetic acid mixture (100 ml); the separated solid was crystallized from a suitable solvent.

13a: Mp.: 190 °C (EtOH); yield: 80%; $C_{18}H_{14}N_2O_2S$ (322.4); calcd.: C 67.1, H 4.38, N 8.7; found: C 66.7, H 4.19, N 8.5.

13b: Mp.: 155 °C (EtOH); yield: 87%; $C_{19}H_{16}N_2O_3S$ (352.4); calcd.: C 64.8, H 4.58, N 8.0; found: C 64.3, H 4.91, N 8.3.

13c: Mp.: 205 °C (EtOH); yield: 75%; $C_{18}H_{13}N_2O_2SCl$ (356.9); calcd.: C 60.6, H 3.67, N 7.9; found: C 60.2, H 3.44, N 7.5.

13a–c: IR (KBr): $\nu = 3400$–3300 (NH), 1680–1670 (C=O), 1650–1645 (C=C), 1620–1600 (C=N) cm^{-1}.

3,5-Dioxo-3,6-dihydro-6-carboxymethyl-1,4-thiazino[3,4-d]-1,3,4-oxadiazole (**14**)

A mixture of **4** (0.01 mol) and maleic anhydride (0.01 mol) in xylene (50 ml) was refluxed for 3 h. The formed solid was crystallized from acetic acid. Mp.: 160 °C; yield: 90%; $C_7H_5N_2O_5S$; calcd.: C 36.7, H 2.19, N 12.2; found: C 36.3, H 2.01, N 11.9; IR (KBr): $\nu = 3400$–2450 (OH carboxylic), 1710 (C=O), 1680 (C=O amide), 1640 (C=C), 1300 (C–O) cm^{-1}.

2,5-bis(2-Methylthio-4H-5-oxo-1,3,4-oxadiazolin-2-yl)-quinol (**15**)

A solution of **4** (0.02 mol) in water (10 ml) was added dropwise to a stirred solution of *p*-benzoquinone (0.01 mol) in water (10 ml). The reaction mixture was stirred at room temperature for 2 h, and the formed solid was crystallized from EtOH. Mp.: 220 °C; yield: 85%; $C_{12}H_{10}N_4O_6S_2$ (370.4); calcd.: C 38.9, H 2.72, N 15.1; found: C 38.7, H 2.49, N 14.7; IR (KBr): $\nu = 3500$ (OH), 3330 (NH), 1695 (C=O), 1615 (C=N), 1280 (C–O) cm^{-1}.

2-(2-Methythio-2,3-dihydro-1,4-naphthoquinon-2-yl)-4H-5-oxo-1,3,4-oxadiazoline (**16**)

A solution of **4** (0.01 mol) in 10 mol) in 10 ml of water and 1,4-naphthoquinone (0.01 mol) in 10 ml of water was treated as described for **15**. Mp.: 205 °C (AcOH); yield: 80%; $C_{13}H_{10}N_2O_4S$ (290.3); calcd.: C 53.8, H 3.47, N 9.7; found: C 53.6, H 3.18, N 9.6.

β-(4H-5-oxo-1,3,4-oxadiazolin-2-methylthio)-propionic acid (**17**)

A mixture of **4** (0.01 mol) and acrylonitrile (0.01 mol) in an ethanol/acetic acid mixture was refluxed for 2 h. The separated solid was crystallized from *n*-propanol. Mp.: 150 °C; yield: 75%; $C_6H_8N_2O_4S$ (204.5); calcd.: C 35.3, H 3.95, N 13.7; found: C 35.0, H 3.49, N 13.4; IR (KBr): $\nu = 3400$–2600 (OH carboxylic), 1750 (C=O nonhydrogen bonded), 1680 (C=O amide), 1620 (C=N), 1200–1100 (C–O) cm^{-1}.

Antimicrobial activity

Test organisms: *Bacillus subtilis* ATCC 66333, *Staphylococcus aureus, Escherichia coli, Pseudomones aeruginosa*; department of microbiology, Faculty of Science, Zagazig University. Culture media: nutrient broth, *Sabouraud*'s broth, nutrient agar, and *Sabouraud*'s agar are products of Oxoide LTD, England. Method: agar plate disc diffusion technique. Standards of 6 mm in diameter sterilized Whatman filter paper discs were impregnated with 10 mg/ml solution of the test compound dissolved in *DMSO* (200 µg/disc) and allowed to dry on air. The discs were applied to the surface of nutrient agar plates seeded with the test organism (each plate contains 15 ml of the agar medium previously seeded with 0.2 ml for 18 h growth culture in liquid media for each organism). The inoculated plates were incubated at 37 °C for 48 h, and the inhibition zone was measured in mm around each disc. Discs impregnated with *DMSO* were used as a control.

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