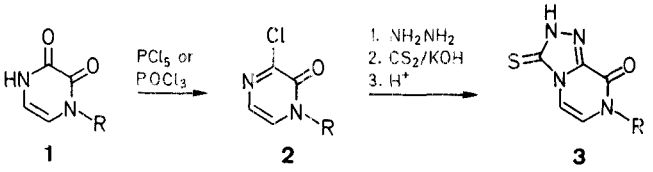
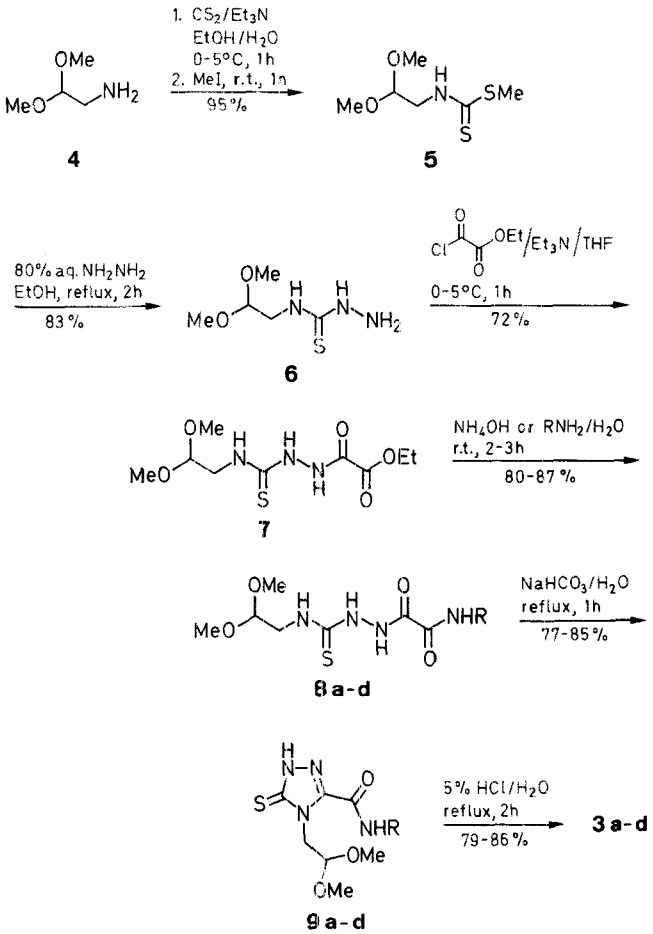


Scheme A

We now describe a new general method of the synthesis of 8-oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazines **3** in synthetically useful yields based upon the simple annulation of the pyrazinone ring onto the triazole ring precursor **9** (Scheme **B**).



3, 8, 9	R
a	H
b	Me
c	Et
d	*c*-Pr

Scheme B

The starting compound, dithiocarbamate **5**, was obtained by treatment of aminoacetaldehyde dimethylacetal **4** with carbon disulfide in the presence of triethylamine and further treatment with methyl iodide in ethanol according to Tsuji et al.[6] This compound was used in the next step without purification by distillation. The reaction of dithiocarbamate **5** with hydrazine monohydrate was carried out in ethanol at reflux temperature and gave a 4-(2,2,-dimethoxyethyl)thiosemicarbazide[7] **(6)** in good yield (83%). The reaction of thiosemicarbazide **6** with

A Novel Convenient Synthesis of 8-Oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazines

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A novel method for the synthesis of 8-oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazines **3** consists of an intramolecular condensation reaction of substituted 1,2,4-triazoline-3-thiones **9**, which possess acetal and aminocarbonyl moieties, with 5% hydrochloric acid. This method is convenient by virtue of its simplicity and the good yields.

In the course of our synthetic work[1] on novel cephalosporin antibiotics, we prepared 8-oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazines **3** which are hydrogen, methyl, ethyl, and cyclopropyl substituted on the pyrazine nitrogen atom.

The one method reported[2] for the preparation of the 3-mercapto-8-oxo-7,8-dihydro-1,2,4-triazolo[4,3-*a*]pyrazine ring system, which is the tautomeric structure of compound **3**, is based on the annulation of the triazole ring onto 2,3(1*H*,4*H*)-pyrazinedione[3] **1** precursor. This method is based upon the reaction of 3-chloro-2(1*H*)-pyrazinone **2** with hydrazine to give the 3-hydrazinopyrazinone, further treatment with carbon disulfide under basic conditions to give the corresponding 3-mercapto-8-oxo-7,8-dihydro-1,2,4-triazolo[4,3-*a*]pyrazines **3** (Scheme **A**). However, this method has some drawbacks that already the preparation of the starting 3-chloro-2(1*H*)-pyrazinones **2** requires several steps and anhydrous reaction conditions.[4] Especially, monochlorination of 2,3-dihydroxypyrazine **1** (R = H) was unsuccessful.[5]

ethyl oxalyl chloride in the presence of triethylamine in tetrahydrofuran afforded a product **7** in 72% yield. The reactions of 1-ethoxyoxalylthiosemicarbazide **7** with excess ammonia or primary amines gave products **8** in good yields (80–87%). On the other hand, the reactions of compound **7** with aniline or 4-methoxyaniline in the absence or presence of *p*-toluenesulfonic acid catalyst were unsuccessful, and only starting compound **7** was recovered.

The well-known cyclization reaction[8–13] of 1-oxamoylthiosemicarbazides **8** was carried out in water using an equimolecular amount of sodium hydrogen carbonate and yielded the previously unreported 5-thioxo-4,5-dihydro-1*H*-1,2,4-triazoles **9** as crystalline solids in good yields (77–85%). Intramolecular condensation reaction[3] of **9**, which possess acetal and aminocarbonyl moieties, with 5% hydrochloric acid at reflux temperature gave 8-oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]-pyrazines **3** in high yields (79–86%). Attempt to achieve a one-pot synthesis of **3** from **7** in water was also very successful (64–69% yields).

Compounds **9** show in the IR spectral absorption due to the C=O stretching at 1658–1686 cm^{-1}, and the C=S stretching at 1264–1280 cm^{-1}, respectively. The ^{1}H-NMR spectrum of **9** is also consistent with a wholly thione structure without evidence for the presence of the thiol tautomer. These values are in good agreement with those reported for the similar system.[14] Structural elucidation of **3** is accomplished on the basis of spectral data[15] and microanalyses. The IR spectra show absorption in the C=O and C=S stretching region 1674–1689 cm^{-1} and 1281–1289 cm^{-1}, respectively. The ^{1}H-NMR spectrum of **3** is also consistent with a thione structure. All compounds show a molecular ion as base peak in the mass spectra.

In conclusion, the present method is convenient in terms of simplicity, easy handling, good yields, and short reaction times. It may be applied to large-scale production, and it may also be applied to other heterocyclic systems. There are some limitations as regards the reactivity of compound **7** with aromatic amines in the reaction of **7** → **8**.

Table 1. Yields, Physical and Spectral Data of 1-Oxamoylthiosemicarbazides **8**

Product	Reaction Time (h)	Yield[a] (%)	mp (°C) (EtOH)	Molecular Formula[b]	^{1}H-NMR (DMSO-d^6/TMS)[c] δ, J(Hz)
8a	2	80	172–173	$C_7H_{14}N_4O_4S$ (250.3)	3.29 (s, 6H, OCH_3); 3.49 (t, 2H, J = 5.6, CH_2); 4.56 (t, 1H, J = 5.2, CH); 8.01 (m, 3H, NH + NH_2); 9.92 (br s, 2H, NHNH)
8b	2	83	167–168	$C_8H_{16}N_4O_4S$ (264.3)	2.66 (d, 3H, J = 4.7, CH_3); 3.29 (s, 6H, OCH_3); 3.50 (t, 2H, J = 5.6, CH_2); 4.56 (t, 1H, J = 5.2, CH); 8.00 (br t, 1H, NH); 8.73 (br q, 1H, CONHC); 9.82 (br s, 2H, NHNH)
8c	2	83	136–138	$C_9H_{18}N_4O_4S$ (278.3)	1.06 (t, 3H, J = 7.1, CH_3); 3.23 (m, 2H, NCH_2); 3.29 (s, 6H, OCH_3); 3.49 (t, 2H, J = 5.6, CH_2); 4.56 (t, 1H, J = 5.2, CH); 8.03 (br s, 1H, NH); 8.79 (br t, 1H, CONHC); 9.52 (br s, 2H, NHNH)
8d	3	87	162–163	$C_{10}H_{18}N_4O_4S$ (290.3)	0.66 (m, 4H, Cp); 2.76 (m, 1H, Cp); 3.30 (s, 6H, OCH_3); 3.53 (t, 2H, J = 5.6, CH_2); 4.62 (t, 1H, J = 5.2, CH); 8.06 (br t, 1H, NH); 8.89 (d, 1H, J = 5.2, CONHC); 10.09 (br s, 2H, NHNH)[d]

[a] Yield of isolated pure product.
[b] Satisfactory microanalyses obtained: C ±0.2, H ±0.1, N ±0.1.
[c] Recorded on a Varian EM-360A spectrometer.
[d] Cyclopropyl.

Table 2. Yields, Physical and Spectral Data of 5-Thioxo-4,5-dihydro-1*H*-1,2,4-triazole **9**

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) $\nu_{C=O,C=S}$ (cm^{-1})	^{1}H-NMR (DMSO-d^6/TMS)[c] δ, J(Hz)	MS (70 eV) m/z (%)
9a	77	193–194 (EtOH)	$C_7H_{12}N_4O_3S$ (232.2)	1674, 1280	3.27 (s, 6H, OCH_3); 4.46 (d, 2H, J = 5.6, CH_2); 4.71 (t, 1H, J = 5.7, CH); 7.97, 8.31 (s, 1H each, NH_2); 13.2 (br s, 1H, H-2)	232 (M^+, 21); 201 (27); 184 (10); 169 (11); 89 (22); 88 (100); 75 (42); 58 (13); 44 (10)
9b	82	179–180 (EtOH)	$C_8H_{14}N_4O_3S$ (246.3)	1677, 1264	2.73 (d, 3H, J = 4.7, CH_3); 3.26 (s, 6H, OCH_3); 4.46 (d, 2H, J = 5.2, CH_2); 4.70 (t, 1H, J = 5.7, CH); 8.86 (br q, 1H, NH); 13.5 (br s, 1H, H-2)	246 (M^+, 16); 215 (16); 89 (22); 88 (100); 75 (58); 59 (13); 58 (52); 55 (12); 47 (17); 43 (18)
9c	81	136–137 (H_2O)	$C_9H_{16}N_4O_3S$ (260.3)	1686, 1276	1.10 (t, 3H, J = 7.0, CH_3); 3.19 (m, 2H, NCH_2); 3.23 (s, 6H, OCH_3); 4.46 (d, 2H, J = 5.2, CH_2); 4.60 (t, 1H, J = 5.0, CH); 8.92 (br t, 1H, NH); 13.2 (br s, 1H, H-2)	260 (M^+, 12); 229 (18); 89 (28); 88 (100); 75 (45); 58 (17); 47 (12); 43 (15)
9d	85	158–159 (EtOH/ EtOAc)	$C_{10}H_{16}N_4O_3S$ (272.3)	1658, 1265	0.63 (m, 4H, Cp); 2.82 (m, 1H, Cp); 3.29 (s, 6H, OCH_3); 4.43 (d, 2H, J = 5.2, CH_2); 4.63 (t, 1H, J = 5.0, CH); 9.08 (br d, 1H, NH); 14.1 (br s, 1H, H-2)[d]	272 (M^+, 13); 241 (11); 128 (11); 89 (23); 88 (100); 75 (43); 58 (16); 56 (11); 47 (12); 43 (10)

[a] Yield of isolated pure product.
[b] Satisfactory microanalyses obtained: C ±0.1, H ±0.1, N ±0.1.
[c] Recorded on a Varian EM-360A spectrometer.
[d] Cyclopropyl.

Table 3. Yields, Physical and Spectral Data of 8-Oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazines **3**

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) $\nu_{C=O,C=S}$ (cm^{-1})	^{1}H-NMR (DMSO-d^6/TMS)[c], δ, J(Hz)	MS (70 eV) m/z (%)
3a	79	>290 (H_2O)	$C_5H_4N_4OS$ (168.1)	1689, 1289	6.89 (t, 1H, J = 5.0, H-6); 7.17 (d, 1H, J = 5.8, H-5); 11.47 (s, 1H, H-7); 14.76 (br s, 1H, H-2)	168 (M^+, 100); 110 (11); 82 (11)
3b	86	>290 (EtOH)	$C_6H_6N_4OS$ (182.2)	1681, 1282	3.41 (s, 3H, CH_3); 7.12 (d, 1H, J = 5.6, H-6); 7.25 (d, 1H, J = 5.8, H-5); 14.54 (br s, 1H, H-2)	182 (M^+, 100); 124 (15); 96 (16); 94 (12); 59 (13); 42 (28)
3c	83	285–286 (EtOH)	$C_7H_8N_4OS$ (196.2)	1674, 1280	1.25 (t, 3H, J = 7.1, CH_3); 3.91 (q, 2H, J = 7.1, CH_2); 7.20 (d, 1H, J = 5.9, H-6); 7.27 (d, 1H, J = 5.8, H-5); 14.75 (br s, 1H, H-2)	196 (M^+, 100); 168 (26); 110 (23); 109 (12); 83 (12); 82 (20); 68 (10); 59 (14); 56 (17); 54 (12)
3d	84	279–280 (EtOH)	$C_8H_8N_4OS$ (208.2)	1678, 1281	0.96 (m, 4H, Cp); 3.23 (m, 1H, Cp); 7.02 (d, 1H, J = 6.0, H-6); 7.20 (d, 1H, J = 6.0, H-5); 13.85 (br s, 1H, H-2)[d]	208 (M^+, 100); 207 (14); 122 (19); 121 (16); 120 (26); 95 (11); 94 (13); 80 (16); 68 (12); 59 (21)

[a] Yield of isolated pure product.
[b] Satisfactory microanalyses obtained: C ±0.2, H ±0.2, N ±0.2.
[c] Recorded on a Bruker AM-200 spectrometer.
[d] Cyclopropyl.

All reagents were of commercial quality from freshly opened containers. Aminoacetaldehyde dimethylacetal, MeI, hydrazine monohydrate, ethyl oxalyl chloride, Et_3N, 2-butanone, $MeNH_2$ (40 wt. % solution in water, $EtNH_2$ (70 wt. % solution in water), and cyclopropylamine were purchased from Aldrich Chemical Co. Reagent quality solvents were used without further purification except THF. Analytical TLC plates and silica gel (230–400 mesh) were purchased from EM Reagents. Melting points were taken using a Electrothermal melting point apparatus and are uncorrected. Microanalysis were obtained using a Perkin-Elmer 240 DS element analyzer. Mass spectra were obtained using a Hewlett Packard model 5985 B spectrometer. IR spectra were recorded on a Analect FX 6160 Infrared spectrophotometer; only the strongest and/or structurally most important peaks are given. ^{1}H-NMR spectra were measured on either a Bruker AM-200 or a Varian EM-360 A spectrometer.

Methyl *N*-(2,2-Dimethoxyethyl)dithiocarbamate (5):
To a stirred solution of aminoacetaldehyde dimethylacetal (21.0 g, 200 mmol) in EtOH (150 mL) and water (10 mL) is added Et_3N (24.3 g, 240 mmol) and CS_2 (16.8 g, 220 mmol) in a dropwise manner at 0–5 °C. The mixture is stirred for 1 h at ambient temperature, then MeI (31.2 g, 220 mmol) is added, stirring is continued for 1 h at r.t. The reaction mixture is concentrated under reduced pressure, and the residue is treated with Et_2O (200 mL). The precipitated crystalline solid ($Et_3N \cdot HI$) is filtered off, and the filtrate is evaporated under reduced pressure to give **5** as slighly yellow liquid, which is subjected to the next reaction without further purification; yield: 36.9 g (95%). An analytical sample is prepared by column chromatography on silica gel (hexane/EtOAc; 2:1).

$C_6H_{13}NO_2S$ (195.3) calc. C 36.90 H 6.71 N 7.17; found 36.84 6.77 7.13

MS (70 eV): m/z = 195 (M^+), 164, 132, 116, 88, 75, 58, 47.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.32 (s, 3H, SCH_3); 3.11 (s, 6H, OCH_3); 3.57 (t, 2H, J = 5.1 Hz, CH_2); 4.28 (t, 1H, J = 5.1 Hz, CH); 7.50 (br s, 1H, NH).

4-(2,2-Dimethoxyethyl)thiosemicarbazide (6):
To a stirred solution of methyl *N*-(2,2-dimethoxyethyl)dithiocarbamate (**5**; 19.5 g, 100 mmol) in EtOH (100 mL) is added 80% aq. NH_2NH_2 (6.9 g, 110 mmol). The mixture is heated at reflux temperature for 2 h, then concentrated under reduced pressure. The residual material is treated with EtOAc (30 mL) and Et_2O (100 mL). The precipitated crystalline solid is separated by filtration and recrystallized from EtOAc and Et_2O to give **6** as colorless crystals; yield: 14.9 g (83%); mp 70 °C (EtOAc/Et_2O).

$C_5H_{13}N_3O_2S$ (179.2) calc. C 33.51 H 7.31 N 23.44; found 33.66 7.44 23.47

MS (70 eV): m/z = 179 (M^+), 147, 116, 88, 75, 58, 47, 31.

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.43 (s, 6H, OCH_3); 3.77 (t, 2H, J = 5.5 Hz, CH_2); 4.06 (s, 2H, NH_2); 4.53 (t, 1H, J = 5.2 Hz, CH); 7.67 (br t, 1H, J = 5.4 Hz, NH); 8.41 (s, 1H, NHN).

4-(2,2-Dimethoxyethyl)-1-(ethoxyoxalyl)thiosemicarbazide (7):
To a stirred solution of thiosemicarbazide **6** (17.9 g, 100 mmol) in THF (150 mL) is added Et_3N (11.1 g, 110 mmol) and EtO_2CCOCl (14.3 g, 105 mmol) in a dropwise manner at 0–5 °C. After stirring for 1 h at ambient temperature, the precipitated solid ($Et_3N \cdot HCl$) is filtered off, and the filtrate is concentrated under reduced pressure. The residual material is crystallized with Et_2O (100 mL), separated by filtration, and recrystallized from EtOH to give **7** as colorless crystals; yield: 20.1 g (72%); mp 122–123 °C (EtOH).

$C_9H_{17}N_3O_5S$ (279.3) calc. C 38.70 H 6.13 N 15.04; found 38.73 6.20 15.09

MS (70 eV): m/z = 279 (M^+), 247, 201, 174, 142, 116, 99, 88, 75, 58.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.39 (t, 3H, J = 7.1 Hz, CH_3); 3.43 (s, 6H, OCH_3); 3.76 (t, 2H, J = 5.4 Hz, CH_2); 4.40 (q, 2H, J = 7.1 Hz, OCH_2); 4.50 (t, 1H, J = 5.1 Hz, CH); 7.26 (br t, 1H, NH); 9.76 (br s, CSNHN); 10.36 (br s, 1H, NNHCO).

4-(2,2-Dimethoxyethyl)-1-(oxamoyl)thiosemicarbazides (8); General Procedure:
To a stirred solution of 4-(2,2-dimethoxyethyl)-1-(ethoxyoxalyl)thiosemicarbazide (**7**; 2.79 g, 10 mmol) in water (20 mL) is added NH_4OH (30 mmol) or the appropriate amine (30 mmol). The reaction mixture is stirred at r.t. for the time indicated in Table 1. The solvent is removed off under reduced pressure, and the residual material is dissolved in EtOH (20 mL). Again, EtOH is evaporated under reduced pressure, and the resultant residue is treated with Et_2O (20 mL). The precipitated solid is collected by filtration, dried, and recrystallized from EtOH to give **8** as colorless crystals (Table 1).

3-*N*-Alkylcarbamoyl-4-(2,2-dimethoxyethyl)-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole (9); General Procedure:
To a stirred suspension of the appropriate 1-oxamoylthiosemicarbazide **8** (10 mmol) in water (20 mL) is added $NaHCO_3$ (0.92 g, 11 mmol). The reaction mixture is stirred at reflux temperature for 1 h. After cooling, the reaction mixture is neutralized with 5% HCl (to pH = 5). The white precipitated solid **9** is separated by filtration, and the mother liquor is extracted with 2-butanone (3 × 10 mL). The extract is dried ($MgSO_4$), and concentrated under reduced pressure to yield an additional amount of the **9**. An analytical sample is prepared by recrystallization from the appropriate solvent (Table 2).

8-Oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazines (3); General Procedure:
To a stirred suspension of the appropriate 5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole **9** (5 mmol) in water (20 mL) is added 5% HCl (5.5 mL, 7.5 mmol). The reaction mixture is stirred at reflux temperature for 2 h. After cooling, the precipitated solid, which is gradually separated during the reaction, is filtered off, washed with cold water (5 mL), and recrystallized from the appropriate solvent to give **3** (Table 3).

One-Pot Synthesis of 3- from 7; General Procedure:
To a stirred solution of 4-(2,2-dimethoxyethyl)-1-(ethoxyoxalyl)thiosemicarbazide (**7**; 2.79 g, 10 mmol) in water (20 mL) is added NH_4OH

(30 mmol) or the appropriate amine (30 mmol). The reaction mixture is stirred at r.t. for 2–3 h, and the excess amine is removed off under reduced pressure. $NaHCO_3$ (0.92 g, 11 mmol) is added to the above mixture, and stirring is continued at reflux temperature for 1 h. After cooling, the reaction mixture is treated with 5% HCl (19 mL, 26 mmol), and stirring is continued at reflux temperature for 2 h. The reaction mixture is cooled, and the precipitated solid, which is gradually separated during the reaction, is filtered off, washed with cold water (5 mL) and dried *in vacuo* to give **3**.

Yields: **3a**: 1.13 g (64%); **3b**: 1.26 g (69%); **3c**: 1.33 g (68%); **3d**: 1.40 g (67%).

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