Ring Chain Transformations. XIV [1]. 3-(ω-Aminoalkyl)-1,2,4-triazoles by Reaction of Isothiosemicarbazides with Lactam Acetals or Lactim Ethers

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Isothiosemicarbazide hydrohalides **1** react with lactam acetals **2** or lactim ethers **3** by the formation of lactamisothiosemicarbazones **4** or ring transformed 3-(ω-aminoalkyl)-1,2,4-triazoles **6**. The latter can independently by synthesized by alkylation of lactamthiosemicarbazones **9**. Condensation of primary 3-(ω-aminoalkyl)-1,2,4-triazoles **6** with lactim ethers **7** can lead to 3-lactamiminoalkyl-1,2,4-triazoles **8**.

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Recently thiocarbonic acid hydrazide derivatives were reported to react as S-C-N-N building block with lactam acetals **2** or lactim ethers **3** giving rise to the formation of 2-(ω-aminoalkyl)-1,3,4-thiadiazoles [2], which showed an interesting *p*H-dependent ring chain tautomerism. The first step of the reaction sequence was the condensation of the lactam derivative with the hydrazine moiety. We now report on reactions of isothiosemicarbazide derivatives **1** with lactam derivatives **2** and **3**. The *S*-alkylisothiosemicarbazides **1** have two nucleophilic sites at the terminal nitrogen atoms. In a number of cases even under mild conditions these reactants **1** react with lactam derivatives **2** or **3** at both nucleophilic centers giving ring transformed 3-(ω-aminoalkyl)-1,2,4-triazoles **6** without intermediates, such as lactamhydrazones **4** or spiro compounds **5**, being isolated. Comparable formation of 3-(ω-hydroxy) or 3-(ω-mercaptoalkyl)-1,2,4-triazoles had been observed in known reactions of aminoguanidines with butyrolactone or butyrothiolactone [3,4,5]. If an excess of lactim ethers **3** were reacted with *S*-alkylisothiosemicarbazides **1** further reaction of the primary ω-amino group of the triazoles **6** (R^3 = H) could be attained. 3-(ω-Lactamiminoalkyl)-1,2,4-triazoles **8** were formed as far as R^1 is methyl or phenyl but not hydrogen. It was also possible to synthesize an ω-lactamiminoalkyl-1,2,4-triazole (**8a**) deriving from different lactam moieties (n ≠ m) by isolating the primary aminoalkyltriazole **6a** and treating it with a lactim ether **7** different from **3** (m ≠ n). The success of the synthesis of ω-functionalized 3-alkyl-1,2,4-triazoles **6** and **8** strongly depends on the nature of substituents R^1, R^2, R^3 and the size of the starting lactam ring (*i.e.* n). Thus, in a number of cases, only condensation products **4** were obtained. The latter could not be transformed into the corresponding 1,2,4-triazoles **6** *e.g.* by raising the reaction temperature or adding an acid. Higher temperatures are known to cause cyclization of lactam hydrazone derivatives **4** by elimination of alkylthiol giving condensed triazoles [6].

We further succeeded in finding an independent synthesis (method F) of the ω-methylaminopropyl-1,2,4-triazole **6f** by reaction of the known thiosemicarbazone **9** (R^1 = R^3 = CH_3, n = 1) [2] with methyl iodide.

All isothiosemicarbazide derivatives **4**, 1,2,4-triazoles **6**

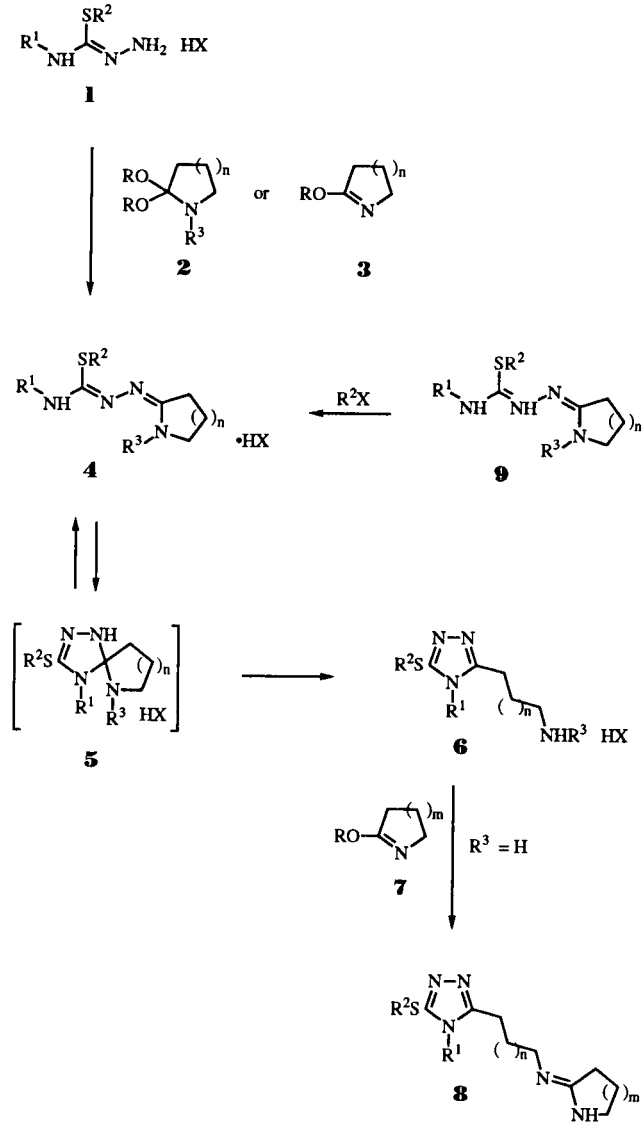

Table 1

Isothiosemicarbazide Derivatives 4, 3-(ω-Aminoalkyl)-1,2,4-triazole Hydrohalides **6** and 3-(ω-Lactaminoalkyl)-1,2,4-triazoles **8**

Compound	(%) Yield/ Method	Mp (°C)	Molecular Formula	^{1}H-NMR δ, J (Hz) [DMSO-d_6]
4b [a]	34/C	171-173 (EtOH)	$C_{12}H_{16}BrN_5O_2S$ (374.3)	2.15 (m, 2H, CH_2), 3.00 (m, 2H, CH_2), 3.62 (m, 2H, CH_2), 4.50 (s, 2H, SCH_2), 7.30 (s, 2H, NH), 7.62 (d, 2H, J = 9 Hz, C_6H_4), 8.15 (d, 2H, J = 9 Hz, C_6H_4), 9.50 (s, 1H, NH), 11.66 (s, 1H, NH)
4d [b]	71/D	128-132 (MeCN)	$C_8H_{17}IN_4S$ (328.2)	[c] 1.97 (m, 6H, $3CH_2$), 2.95 (m, 5H, SCH_3, CH_2), 3.80 (m, 2H, CH_2)
4i [d]	51/C	161-163 (EtOH)	$C_{15}H_{21}N_5O_2S$ (335.4)	[e] 1.16 (t, 3H, J = 7 Hz, CH_3), 1.92 (p, 2H, J = 8 Hz, CH_2), 2.68 (t, 2 Hz, J = 8 Hz, CH_2), 2.85 (s, 3H, NCH_3), 3.28 (m, 4H, $2CH_2$), 4.34 (s, 2H, SCH_2), 5.96 (t, 1H, NH), 7.58 (d, 2H, J = 9 Hz, C_6H_4), 8.12 (d, 2H, J = 9 Hz, C_6H_4)
4k	69/B	154-155 (MeCN)	$C_{13}H_{19}IN_4S$ (390.3)	1.78 (s, 4H, $2CH_2$), 2.51 (m, 5H, SCH_3, CH_2), 3.20 (m, 2H, CH_2), 7.35 (m, 6H, C_6H_5, NH), 8.96 (m, 2H, NH)
6a [f]	54/A	199-201 (EtOH)	$C_6H_{13}IN_4S$ (300.2)	2.48 (m, 2H, CH_2), 2.79 (s, 3H, SCH_3), 3.12 (m, 4H, $2CH_2$)
6c	73/A	206-208 (MeCN)	$C_7H_{15}IN_4S$ (314.2)	1.63 (m, 4H, 2 CH_2), 2.51 (s, 3H, SCH_3), 2.85 (m, 4H, $2CH_2$), 9.03 (br, 1H, NH)
6e	38/B	154-156 (2-PrOH)	$C_7H_{15}IN_4S$ (314.2)	2.11 (m, 2H, CH_2), 2.62 (s, 3H, SCH_3), 2.95 (m, 4H, $2CH_2$), 2.53 (s, 3H, SCH_3)
6f	64/C 56/F	177-179 (MeCN)	$C_8H_{17}IN_4S$ (328.2)	2.11 (m, 2H, CH_2), 2.51 (m, 6H, NCH_3, SCH_3), 2.81 (m, 2H, CH_2), 3.05 (m, 2H, CH_2), 3.74 (s, 3H, NCH_3)
6g [g]	60/A	168-170 (2-PrOH)	$C_8H_{17}IN_4S$ (328.2)	1.24 (t, 2H, J = 7 Hz, CH_3), 2.10 (p, 2H, J = 7 Hz, CH_2), 2.61 (s, 3H, SCH_3), 2.90 (m, 4H, $2CH_2$), 3.90 (q, 2H, J = 7 Hz, CH_2), 7.80 (br, 2H, NH)
6h [h]	52/A	173-175 (2-PrOH)	$C_9H_{19}IN_4S$ (342.2)	1.17 (t, 3H, J = 8 Hz, CH_3), 1.30 (t, 3H, J = 8 Hz, CH_3), 2.03 (p, 2H, J = 8 Hz, CH_2), 2.85 (t, 2H, J = 8 Hz, CH_2), 2.98 (t, 2H, J = 8 Hz, CH_2), 3.12 (q, 2H, J = 8 Hz, CH_2), 3.88 (q, 2H, J = 8 Hz, CH_2), 7.73 (s, 3H, NH)
6j	60/B	198-199 (MeCN)	$C_{12}H_{17}IN_4S$ (376.3)	1.91 (q, 2H, J = 7 Hz, CH_2), 2.55 (s, 3H, SCH_3), 2.61 (m, 2H, CH_2), 2.90 (t, 2H, J = 7 Hz, CH_2), 7.59 (m, 6H, C_6H_5, NH)
8a [i]	76/E	140-142 (2-PrOH)	$C_{12}H_{22}IN_5S$ (395.3)	1.66 (m, 6H, $3CH_2$), 1.95 (m, 2H, CH_2), 2.52 (s, 3H, SCH_3), 2.75 (m, 4H, 2 CH_2), 3.24 (m, 2H, CH_2), 3.33 (m, 2H, CH_2)
8e	40/A	224-225 (2-PrOH)	$C_{11}H_{20}IN_5S$ (381.3)	2.09 (m, 4H, $2CH_2$), 2.58 (s, 3H, SCH_3), 2.80 (m, 4H, 2 CH_2), 3.36 (m, 2H, CH_2), 3.49 (s, 3H, NCH_3), 3.62 (m, 2H, CH_2)
8j [j]	96/D	176-177 (MeCN)	$C_{16}H_{22}IN_5S$ (443.3)	[e] 2.25 (m, 4H, $2CH_2$), 2.62 (s, 3H, SCH_3), 2.71 (m, 2H, CH_2), 3.15 (t, 2H, CH_2), 3.60 (m, 2H, CH_2), 3.83 (m, 2H, CH_2), 7.31 (m, 2H, C_6H_5), 7.55 (m, 3H, C_6H_5), 9.86 (br, 1H, NH)

[a] ^{13}C-nmr (DMSO-d_6): δ 28.3 (CH_2), 32.5 (SCH_2), 46.5 (NCH_2), 123.2 (CH), 130.3 (CH), 146.2, 146.5, 154.9, 162.4; ms: (m/z) 293 (M^+, 5), 169 (60), 139 (97), 106 (48), 90 (33), 89 (47), 84 (58), 78 (65), 45 (36), 41 (56), 39 (30), 30 (100). [b] ms: (m/z) 152 (77), 128 (91), 127 (50), 123 (33), 55 (39), 54 (34), 43 (56), 42 (44), 41 (100), 39 (57); 24 uv (methanol): γ max 221 (4.25), 266 nm (3.97). [c] In trifluoroacetic acid. [d] ^{13}C-nmr (DMSO-d_6): δ 16.3 (CH_3), 20.0 (CH_2), 27.4 (CH_2), 31.7 (NCH_3), 32.9 (SCH_2), 37.9 (NCH_2), 52.1 (=C-CH_2N), 123.5 (CH), 123.8 (CH), 129.7 (CH), 130.0 (CH), 147.2, 148.8, 151.8, 164.9; ms: (m/z) 335 (M^+, 7), 136 (40), 116 (34), 98 (100), 89 (34), 78 (48), 70 (42), 69 (43), 55 (67), 43 (38), 42 (40), 30 (74). [e] In deuteriochloroform. [f] ms: (m/z) 172 (M^+ –HI, 4), 142 (49), 129 (93), 128 (50), 30 (100); uv (methanol): γ max 220 nm (4.28). [g] ^{13}C-nmr (DMSO-d_6): δ 14.9 (CH_3), 15.1 (CH_3), 21.4 (CH_2), 24.0 (CH_2), 38.2 (NCH_2), 38.4 (NCH_2), 149.6, 154.3; ms: (m/z) 200 (M^+ –HI, 7), 186 (18), 157 (16), 143 (26), 142 (49), 128 (69), 127 (36), 115 (27), 69 (19), 60 (16), 56 (23), 55 (20), 44 (41), 43 (32), 42 (40), 41 (22), 30 (100), 29 (34). [h] ^{13}C-nmr: δ 14.9 (CH_3), 15.0 (CH_3), 21.4 (CH_2), 23.9 (CH_2), 27.1 (CH_2), 38.3 (NCH_2), 38.3 (NCH_2), 148.4, 154.2; ms: (m/z) 214 (M^+ –HI, 2), 184 (22), 171 (17), 156 (26), 143 (21), 142 (61), 12 (78), 127 (36), 115 (20), 60 (17), 56 (21), 43 (22), 42 (32), 41 (23), 30 (100), 29 (62); corresponding free base: Oil; ^{1}H-nmr (DMSO-d_6): δ 1.30 (m, 6H, $2CH_3$), 1.97 (m, 2H, CH_2), 2.78 (m, 4H, 2 CH_2), 3.10 (q, 2H, J = 7 Hz, SCH_2), 3.92 (q, 2H, J = 7 Hz, NCH_2), 4.34 (s, 3H, SCH_3); ms: (m/z) 214 (M^+, 2), 171 (21), 44 (100), 30 (4). [i] ms: (m/z) 267 (M^+, 5), 139 (100), 96 (92), 55 (30), 41 (35); uv (methanol): γ max 219 nm (4.40); [j] ^{13}C-nmr (DMSO-d_6): δ 14.5 (CH_3), 20.3 (CH_2), 21.8 (CH_2), 24.3 (CH_2), 30.4 (CH_2), 42.3 (CH_2N), 47.1 (=C-CH_2N), 127.1 (CH), 128.1 (CH), 132.7, 150.9, 154.6, 168.2 (N=C-N); ms: (m/z) 315 (M^+, 2), 111 (100), 98 (32).

4	**6**	**8**	R^1	R^2	R^3	n	m	X
	a	**a**	H	Me	H	1	3	I
b			H	4-$NO_2C_6H_4CH_2$	H	1	–	Br
	c		H	Me	H	2	–	I
d			H	Me	H	3	–	I
	e	**e**	Me	Me	H	1	1	I
	f		Me	Me	Me	1	–	I
	g		Et	Me	H	1	–	I
	h		Et	Et	H	1	–	I
i			Et	4-$NO_2C_6H_4CH_2$	Me	1	–	Br
	j	**j**	Ph	Me	H	1	1	I
k			Ph	Me	H	2	–	I

and **8** are new. Their structure is confirmed by spectroscopic data. The differentiation between isomeric structures **4**, **5** and **6** is possible by ^{1}H-nmr and mass spectroscopy like reported earlier for other ω-functionalized alkylheterocycles [7]. The possibility of transforming the ω-aminoalkyl-1,2,4-triazole hydroiodides **6** (X = I) to the corresponding free bases could be demonstrated by treating compound **6h** with aqueous sodium hydroxide. The nmr data of the oily product clearly demonstrate that the free bases of **6** also exist as ω-aminoalkyl-1,2,4-triazoles rather than as isomeric structures **4** or **5**.

Table 2

Compound	Elemental Analyses					
	Calcd.			Found		
	C	H	N	C	H	B
4b	38.51	4.31	18.71	38.67	4.27	18.52
4d	29.28	5.22	17.07	29.31	5.12	17.01
4i	53.71	6.31	20.88	53.53	6.24	20.67
4k	40.01	4.91	14.36	40.14	5.06	14.55
6a	24.01	4.36	18.67	24.51	4.54	18.69
6c	26.76	4.81	17.83	27.23	4.73	18.20
6e	26.76	4.81	17.83	26.66	4.58	17.90
6f	29.28	5.22	17.07	29.75	5.19	17.15
6g	29.28	5.22	17.07	29.19	5.05	17.03
6h	31.58	5.60	16.37	31.29	5.63	16.05
6j	38.31	4.55	14.89	38.54	4.27	14.59
8a	36.46	5.61	17.72	36.82	5.87	17.40
8e	34.65	5.29	18.37	34.91	5.20	18.16
8j	43.34	5.00	15.80	43.90	5.11	16.09

EXPERIMENTAL

The melting points were measured with a "Boetius" hot-stage apparatus and are uncorrected. The ^{1}H-nmr spectra were measured with a Tesla BS 587 (80 MHz) FT or a Bruker AC 300 spectrometer. The ^{13}C-nmr spectra were recorded on a Bruker AC 300. All spectra were taken in DMSO-d_6. Mass spectra were taken with a Hewlett Packard 599 SA spectrometer.

Isothiosemicarbazide Derivatives **4**, 3-(ω-Aminoalkyl)-1,2,4-triazole Hydrohalides **6** and 3-(ω-Lactamiminoalkyl)-1,2,4-triazoles **8**.

Method A.

A mixture of isothiosemicarbazide hydrohalide **1** (0.03 mole), acetonitrile (30 ml) and *O*-lactim methyl ether **3** (R = CH_3) (0.06 mole) is refluxed for 20 minutes (in cases of products **4** for 2 hours). As far as no product precipitates, the solvent is evaporated in vacuum. The remainder is mixed with a small amount of ethanol. The product is filtered by suction and recrystallized.

Method B.

A mixture of isothiosemicarbazide hydrohalide **1** (0.02 mole), acetonitrile (30 ml), and *O*-lactim methyl ether **3** (R = CH_3) (0.03 mole) is stirred at room temperature for 1 hour. After 5 hours standing in a refrigerator the product is filtered by suction and recrystallized.

Method C.

Lactam acetal **2** (0.06 mole) is added dropwise to a mixture of isothiosemicarbazide hydrohalide **1** (0.02 mole) and ethanol (30 ml). After 30 minutes of reflux the mixture is concentrated in vacuum. The product is filtered and recrystallized.

Method D.

A mixture of isothiosemicarbazide hydrohalide **1** (0.02 mole) and *O*-lactim methyl ether **3** (0.05 mole) is refluxed for 2.5 hours. After cooling to room temperature the product is filtered and recrystallized.

Method E.

A mixture of 3-(ω-aminoalkyl)-1,2,4-triazole hydrohalide **6** (0.005 mole), *O*-lactim methyl ether (0.01 mole), and methanol (30 ml) is refluxed for 2 hours. After cooling to -5° the precipitate is filtered off and recrystallized.

Method F.

A mixture of the lactamthiosemicarbazone **9** (0.002 mole), acetonitrile (5 ml) and methyl iodide (5 ml) is refluxed for 10 minutes. After cooling to room temperature the product is filtered by suction and recrystallized.

Liberation of the Free Base of the 3-(ω-Aminoalkyl)-1,2,4-triazole Hydroiodide **6h** (see Table 1, footnote [h]).

Concentrated aqueous sodium hydroxide (0.003 mole) is added to a solution of the hydroiodide **6h** (0.75 g, 0.005 mole) in a small amount of water (about 3 ml). The solution is extracted with diethyl ether. After evaporation of the solvent the remainder is dissolved in hot *n*-hexane. After cooling to room temperature the free base separates as oil.

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