Ring Transformations of Semicyclic 1,3-Dicarbonyl Heteroanalogs; IV[1]. Synthesis of 3-(ω-Aminoalkyl)-1,2,4-thiadiazoles by Ring Transformation Reaction of Semicyclic Thioacylamidines with 3,3-Pentamethyleneoxaziridine

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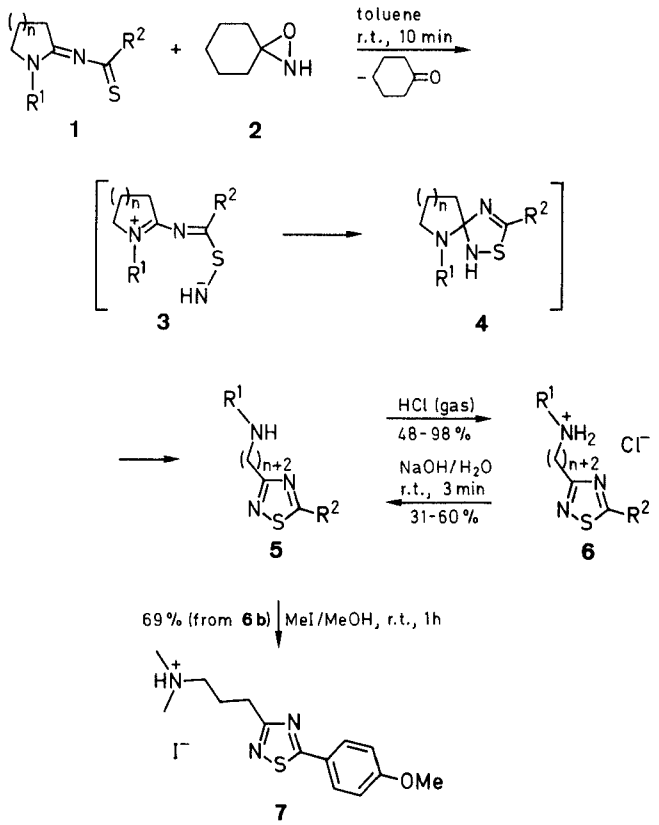
Dedicated to Prof. H.J. Bestmann on the occasion of his 65th birthday

Semicyclic thioacylamidines **1** react with 3,3-pentamethyleneoxaziridine by ring transformation affording novel ω-aminoalkyl-1,2,4-thiadiazoles **5**, which are conveniently isolated as hydrochlorides **6**. These can be transformed to the corresponding free bases **5**, which in one case are methylated at the amino group to give an ω-dimethylaminoalkyl-1,2,4-thiadiazole **7**.

Semicyclic thioacylamidines **1** are easily available from thioamides and in situ generated lactam acetals[2] or by sulfuration of semicyclic *N*-acylamidines with phosphorus pentasulfide.[3] They are bridged heteroanalogs of imides. Depending on the type of reactant, they can serve as either C–N–C or C–N–C–S synthons for heterocyclic products, having an ω-aminoalkyl substituent.[1,3,4] Acidic methyl halides, for example, cause *S*-alkylation and subsequent attack of the deprotonated *S*-methylene group at the amidine *C*-atom. By a ring transformation, ω-aminoalkylthiazoles are formed.[4]

We now report the reaction of semicyclic thioacylamidines **1** with 3,3-pentamethyleneoxaziridine **2**. This compound has proved a versatile aminating reagent[5] for a number of nucleophiles. Its reaction with *N*-thioacylamidines **1** in toluene is very fast, even at room temperature; within a few seconds ω-aminoalkyl-1,2,4-thiadiazoles **5** are formed. These compounds are conveniently isolated as hydrochlorides **6** by the addition of gaseous hydrogen chloride.

TLC-investigations showed that the aminoalkyl-1,2,4-thiadiazole system developed before gaseous hydrogen chloride is added. The formation of ω-aminoalkyl-1,2,4-thiadiazoles **5** and **6** can be explained by primary *S*-amination and subsequent nucleophilic attack of the *S*-amino group at the amidine *C*-atom, giving a ring transformation via spiro intermediates **4**. If semicyclic imidoylthioureas **1** (R = NH_2 or NHaryl) are used in the reaction with pentamethyleneoxaziridine **2**, no crystalline products could be isolated from the above procedure.



1, 3–7	n	R^1	R^2
a	1	Me	4-ClC_6H_4
b	1	Me	4-$MeOC_6H_4$
c	1	Me	4-$Me_2NC_6H_4$
d	1	Me	2-thienyl
e	2	Et	4-ClC_6H_4
f	3	Me	4-ClC_6H_4
g	3	Me	3,4-$(MeO)_2C_6H_3$

The ω-aminoalkyl-1,2,4-thiadiazole hydrochlorides **6** are new compounds which are colorless and crystalline and are very soluble in water. Their structure is confirmed by elemental analyses and spectroscopic methods. In the ^{1}H-NMR spectra, for example, a typical sequence of chemical shifts[3] for the alkyl chain is found ($CH_2\underline{CH_2}CH_2 < CH_2$thiadiazole $< CH_2N$). Molecular peaks in the MS are weak (less than 1 %), indicating easy fragmentation. Fragment peaks of onium cleavage or McLafferty rearrangement typical for ω-aminoalkyl heterocycles,[3] as well as cleavage of the heterocyclic ring to arylcarbonitrile cations are observed. All spectroscopic data rule out possible isomeric structures lacking the ω-aminoalkyl chain such as **3** or **4**.

The free bases **5** are generated by the addition of sodium hydroxide to aqueous solutions of the salts **6**. The former are colorless oils or low melting solids, which are sparingly soluble in water. Potentiometric determination of their pK_a-values revealed that the base strength is similar to that of aliphatic amines. Hence, protonation of the heteroaromatic ring or chelation effects are unlikely for salts **6**. This assumption is supported by ^{13}C-NMR results. Going from the free bases **5** to the salts **6**, the chemical shifts of aromatic carbon atoms are hardly affected, while the alkyl-C atoms suffer a downfield shift of 3–4 ppm, which is typical for the protonation of linear aliphatic amines.[8]

Reaction of the ω-aminoalkyl-1,2,4-thiadiazole **5b** with methyl iodide gives rise to a selective methylation of the ω-amino group. The colorless hygroscopic dimethylaminopropyl-1,2,4-thiadiazole **7** exhibits one signal for the two equivalent methyl groups. UV-absorption is not affected by this methylation. Attempts to achieve ring transformation reactions of the 3-(3-methylaminopropyl)-1,2,4-thiadiazole **(5a)** according to Boulton–Katritzky scheme[9] by prolonged heating in dimethylformamide yielded complex mixtures, containing 4-chlorobenzonitrile.

The synthesis of ω-aminoalkyl-1,2,4-thiadiazoles **5** and **6** is the first example, where the general concept[3] of preparing ω-functionalized alkylheterocycles by ring transformation of semicyclic 1,3-dicarbonyl heteroanalogs has been applied to the 1,2,4-thiadiazole series. So far[10] only one

Table. Compounds **5**, **6**, and **7** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	^{1}H-NMR (DMSO-d_6/TMS) δ, J(Hz)	MS (70 eV) m/z (%)
5a[b]	60	69–71 (hexane)	$C_{12}H_{14}ClN_3S$ (267.8)	1.9 (m, 2H, $NCH_2C\underline{H_2}CH_2$), 2.3 (s, 3H, CH_3), 3.0 (m, 4H, $NC\underline{H_2}CH_2C\underline{H_2}$), 7.6 (d, $2H_{arom}$, $J = 9$), 8.0 (d, $2H_{arom}$, $J = 9$)	267 (M^+), 210 (15), 58 (37), 44 (100)
5b	51	49–51 (hexane)	$C_{13}H_{17}N_3OS$ (263.3)	–	263 (M^+, 3), 206 (45), 134 (36), 44 (100)
5e	31	oil	$C_{14}H_{18}ClN_3S$ (295.8)	–	295 (M^+, 3), 125 (10), 58 (100)
6a[c]	92	185–186 (EtOH)	$C_{12}H_{15}Cl_2N_3S$ (304.2)	2.3 (m, 2H, $NCH_2C\underline{H_2}CH_2$), 2.5 (s, 3H, CH_3), 3.0 (m, 4H, $NC\underline{H_2}CH_2C\underline{H_2}$), 7.5 (d, $2H_{arom}$, $J = 9$), 7.7 (d, $2H_{arom}$, $J = 9$), 9.1 (br, 2H)	268 ($M^+ - Cl$, 0, 1), 224 (4), 210 (22), 130 (10), 112 (5), 58 (37), 44 (100)
6b	98	185–187 (EtOH)	$C_{13}H_{18}ClN_3OS$ (299.8)	2.2 (m, 2H, $NCH_2C\underline{H_2}CH_2$), 2.5 (s, 3H, CH_3), 2.9 (m, 4H, $NC\underline{H_2}CH_2C\underline{H_2}$), 3.8 (s, 3H, OCH_3), 7.1 (d, $2H_{arom}$, $J = 9$), 7.9 (d, $2H_{arom}$, $J = 9$), 9.2 (br, 2H, NH)	263 ($M^+ - Cl$, 0.1), 206 (39), 134 (29), 130 (9), 58 (48), 44 (100)
6c	48	239–240 (EtOH)	$C_{14}H_{21}ClN_4S$ (312.8)	2.2 (m, 2H, $NCH_2C\underline{H_2}CH_2$), 2.5 (m, 2H, $NCH_2CH_2C\underline{H_2}$), 3.0 (s + m, 11H, $NCH_2 + 3CH_3$), 6.8 (d, $2H_{arom}$, $J = 8$), 7.7 (d, $2H_{arom}$, $J = 8$)	276 ($M^+ - Cl$, 3), 219 (45), 152 (13), 146 (38), 129 (13), 44 (100)
6d	84	171–172 (EtOH)	$C_{10}H_{14}ClN_3S$ (275.7)	2.2 (m, 2H, CH_2), 2.5 (s, 2H, CH_3), 3.2 (m, 4H, $2CH_2$), 7.3 (m, $2H_{(thienyl)}$), 7.8 (d, $2H_{thienyl}$, $J = 4$)	239 ($M^+ - Cl$, 0.3), 182 (25), 110 (11), 58 (38), 44 (100)
6e	82	168–170 (EtOH)	$C_{14}H_{19}Cl_2N_3S$ (332.3)	1.25 (t, 3H, $J = 3$, CH_3), 1.8 [m, 4H, $NCH_2(C\underline{H_2})_2CH_2$], 2.9 [m, 6H, $NC\underline{H_2}(CH_2)_2C\underline{H_2} + C\underline{H_2}CH_3$], 7.6 (d, $2H_{arom}$, $J = 9$), 8.0 (d, $2H_{arom}$, $J = 9$)	295 ($M^+ - Cl$, 2), 137 (4), 125 (10), 58 (100), 44 (13)
6f[d]	78	127–129 (EtOH)	$C_{14}H_{19}Cl_2N_3S$ (332.3)	1.8 (m, 6H, $NCH_2(C\underline{H_2})_3CH_2$], 3.2 (s, 3H, CH_3), 3.7 [m, 4H, $NC\underline{H_2}(CH_2)_3C\underline{H_2}$), 9.7 (d, $2H_{arom}$, $J = 9$), 10.1 (d, $2H_{arom}$, $J = 9$)	295 ($M^+ - Cl$, 1), 264 (3), 223 (5), 125 (5), 115 (13), 44 (100)
6g	68	156–158 (EtOH)	$C_{17}H_{26}ClN_3O_2S$ (371.9)	–	335 (M^+, 1), 236 (4), 163 (10), 58 (100)
7a[e]	69	208–209 (MeOH)	$C_{14}H_{20}IN_3OS$ (405.3)	2.0 (m, 2H, $NCH_2C\underline{H_2}CH_2$), 2.8 [s, 6H, $N(CH_3)_2$], 3.0 (m, 4H, $NC\underline{H_2}CH_2C\underline{H_2}$), 3.8 (s, 3H, OCH_3), 7.5 (d, $2H_{arom}$, $J = 8$), 7.9 (d, $2H_{arom}$, $J = 8$)	237 (7), 142 (14), 72 (27), 58 (100)

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.3, N ±0.3. Exception **5b**, C 0.34.
[b] ^{13}C-NMR (DMSO-d_6): δ = 27.6, 30.3, 36.0, 50.8, 128.6, 128.8, 129.5, 136.7, 177.6, 185.8
UV (MeOH): λ_{max} (log ε) = 219 (4.02), 305 nm (4.31); pK_B (MeOH/H_2O) = 3.8.
[c] ^{13}C-NMR (DMSO-d_6): δ = 23.8, 29.5, 32.3, 47.7, 126.6, 128.5, 129.0, 136.8, 176.2, 186.2.
[d] ^{13}C-NMR (DMSO-d_6): δ = 21.5, 24.8, 25.4, 26.9, 32.0, 47.8, 128.6, 129.0, 136.7, 177.3, 186.0.
[e] UV (MeOH): λ_{max} (log ε) = 221 (4.33), 305 nm (4.24).

synthesis is known, where the 1,2,4-thiadiazole ring is formed from a C–N–C–S– and a N-synthon.[6] In this case nonbridged *N*-thioacylamidines were reacted with hydroxylamine-*O*-sulfonic acid giving 1,2,4-thiadiazoles lacking an ω-aminoalkyl group.[6] The successful synthesis of ω-aminoalkyl-1,2,4-thiadiazoles further demonstrates once more the versatility of 3,3-pentamethyleneoxaziridine as aminating reagent.

Melting points are uncorrected and were measured using a Boetius heating block apparatus. ^{1}H-NMR were measured at 80 MHz on a Tesla BS 587 FT-spectrometer. Mass spectra were recorded on a Hewlett Packard 599 SA spectrometer.

3-(ω-Aminoalkyl)-1,2,4-thiadiazoles 5; General Procedure:
3-(ω-Aminoalkyl)-1,2,4-thiadiazole hydrochloride **6** (0.01 mol) (see below) is dissolved in a minimum amount of water (about (~ 2 mL). A solution of NaOH (0.5 g) in water (2 mL) is added. The product is either collected by suction filtration or is extracted with Et_2O. After evaporation of the solvent the product is purified by recrystallization (Table).

3-(ω-Aminoalkyl)-1,2,4-thiadiazole Hydrochlorides 6; General Procedure:
Semicyclic thioacylamidine **1**[2,3] (0.01 mol) is added to a solution of 3,3-pentamethyleneoxaziridine (0.015 mol) in toluene (~ 50 mL) and the mixture is stirred well. After 10 min gaseous HCl is introduced till all the product has precipitated. It is filtered by suction and recrystallized from EtOH.

3-(3-Dimethylaminopropyl)-5-(4-methoxyphenyl)-1,2,4-thiadiazole Hydroiodide (7a):
MeI (1.4 g, 0.01 mol) is added to a solution of 3-(3-methylaminopropyl)-5-(4-methoxyphenyl)-1,2,4-thiadiazole **(5b)** (1.3 g, 0.005 mol) in MeOH (20 mL). After stirring for 1 h at r.t. the product is filtered and recrystallized from MeOH.

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