Ring Transformations via Bridged 1,3-Dicarbonyl Heteroanalogs; Part II.[1]. Synthesis of 4-(ω-Aminoalkyl)-thiazoles by a Novel Ring Transformation Reaction of Semicyclic Thioacylamidines with Acidic Methyl Halides

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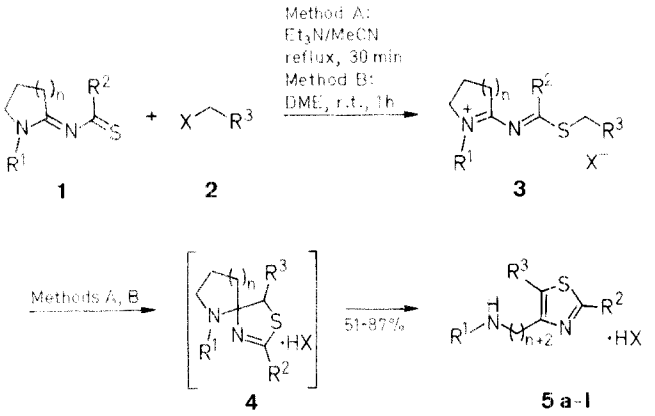
Semicyclic *N'*-(thioacyl)amidines **1** react with acidic methyl halides **2** as C-synthons via *S*-alkylation and cyclization to give 4-(ω-aminoalkyl)-thiazole hydrohalides **5**. In this transformation, the thiazole ring is formed while the initial lactam ring is opened. In contrast, semicyclic *N'*-(thioacyl)amidines **1** react with α-haloketones as C–C building blocks in a Hantzsch-type thiazole synthesis affording semicyclic 2-aminothiazoles **6** or thiazolium salt **7** while the starting lactamimine ring is retained.

N'-Thioacylamides[2–5] and their derivatives such as *N'*-thioacylamidines[6–8] or *N*-thioacylimidoyl chlorides[9] are of wide interest as synthetic intermediates in heterocyclic synthesis. For example, these compounds can be used as S–C–N–C building blocks for thiazole rings if they are submitted to the reaction with methyl halides **2** which activated by an electron-withdrawing substituent R[3].[3,6,8,10–12]

Continuing our research on *N*-thioacylamide derivatives we have recently succeeded in converting thioamides or thioureas into semicyclic *N'*-thiocarbonylamidines **1** (R^2 = aryl, NH-aryl, or NH_2) which represent bridged *N'*-thioacylamidines.[1,13] We now report on reactions of these compounds **1** with acceptor-substituted methyl halides **2**. A peculiar feature is that the amino leaving group of the semicyclic thioacylamidines **1** is connected to the amidine C-atom directly by a C–N bond as well as via the alkylene bridge $(CH_2)_{n+2}$. Hence nucleophilic attack at the amidine C-atom does not lead to elimination of an amine but to cleavage of the lactam ring with the leaving amino group remaining connected to the amidine C-atom by an alkyl chain $(CH_2)_{n+2}$. Thus, the reaction of compounds **1** with methyl halides **2** should produce 4-(ω-aminoalkyl)thiazoles **5** by an *S*-alkylation, deprotonation, cyclization, and elimination sequence. Our experiments showed that the reaction of **1** with **2** [R^3 = aryl, heteroaryl, COR[4], CN, NO_2, C(Ph)=C(CN)$_2$] in polar solvents at elevated temperatures usually leads to the formation of the hydrohalides **5** of 4-(ω-aminoalkyl)thiazoles in high yields, in some cases even in the absence of an additional base such as triethylamine.[14] In the absence of base it is also possible to isolate some intermediate *S*-alkylation products **3** (for one example, **3a** see footnote in the Table) or mixtures of thiazoles **5** and their spiro precursors **4**. The latter can be detected in the ^{1}H-NMR spectra by a CHS singlet at about δ = 5 (for example **4g**/**5g**: δ = 5.0 in DMSO-d_6).



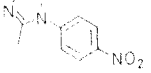
3,4,5	R^1	R^2	R^3	n	X
a	Me	NH_2	4-$NO_2C_6H_4$	1	Br
b	Me	PhNH	4-$NO_2C_6H_4$	1	Br
c	Me	PhNH	2-C_5H_4N	1	Cl
d	Me	PhNH	NO_2	1	Br
e	Me	4-$MeOC_6H_4$		1	Cl
f	Me	4-$MeOC_6H_4$	PhCO	1	Br
g	Me	4-$MeOC_6H_4$	4-BrC_6H_4CO	1	Br
h	Me	4-$MeOC_6H_4$	CN	1	Cl
i	Me	4-$MeOC_6H_4$		1	Br
j	Et	4-$MeOC_6H_4$	4-BrC_6H_4CO	2	Br
k	H	EtNH	4-$NO_2C_6H_4$	3	Br
l	Me	PhNH	4-$NO_2C_6H_4$	3	Br

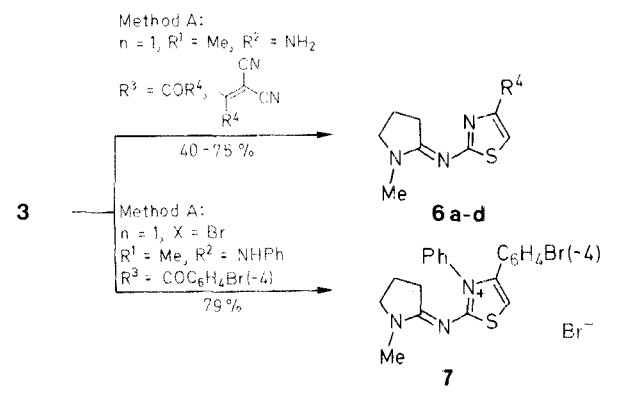
Table. Compounds **5**, **6**, and **7** Prepared

Product	Yield (%)/ Method	mp (°C)[a] (solvent)	Molecular Formula[b]	MS (70 eV)[c] *m/z* (%)	^{1}H-NMR (DMSO-d_6/TMS)[c] δ, *J* (Hz)
5a[e]	85/A	280–282 (DMF)	$C_{13}H_{17}BrN_4O_2S$ (373.4)	292 (M^+ – HBr, 15), 249 (15), 248 (34), 236 (16), 235 (78), 44 (100)	2.0 (m, 2H, $CH_2CH_2CH_2$); 2.5 (s, 3H, NCH_3); 2.87 (m, 4H, CH_2N, CH_2C); 4.6 (br, 2H, NH_2); 7.31 (s, 1H, NH); 7.4 (d, 2H, *J* = 9, C_6H_4); 8.1 (d, 2H, *J* = 9, C_6H_4)
5b[f]	80/A	235–237 (MeCN/ AcOH)	$C_{19}H_{21}BrN_4O_2S$ (449.4)	368 (M^+ – HBr, 15), 324 (32), 311 (100), 278 (14), 77 (18), 44 (50)	2.0 (m, 2H, $CH_2CH_2CH_2$); 2.43 (s, 3H, NCH_3); 2.81 (m, 4H, CH_2N, CH_2C); 6.9–7.2 (m, 3H, C_6H_5); 7.5 (m, 2H, C_6H_5); 7.6 (d, 2H, *J* = 9, C_6H_4); 8.1 (d, 2H, *J* = 9, C_6H_4)
5c	73/A	110–112 ($CHCl_3$)	$C_{18}H_{21}ClN_4S$ (360.9)	280 (25), 267 (71), 117 (19), 78 (34), 51 (20), 44 (100)	2.12 (m, 2H, $CH_2CH_2CH_2$); 2.43 (s, 3H, NCH_3); 2.94 (m, 4H, CH_2N, CH_2C); 7.4–7.8 (m, 8H, C_6H_5, C_5H_4N); 8.43 (d, 1H, C_6H_4N); 9.06 (s, 1H, NH); 10.5 (s, 1H, NH)
5d[g]	68/A	208–210 (MeOH)	$C_{13}H_{17}BrN_4O_2S$ (373.3)	292 (M^+ – HBr, 0.1), 258 (3), 230 (12), 226 (35), 200 (20), 141 (10), 135 (76), 82 (100)	[h]2.0 (m, 2H, $CH_2CH_2CH_2$); 2.5 (s, 3H, NCH_3); 3.02 (m, 4H, CH_2N, CH_2C); 7.41 (m, 5H, C_6H_5); 8.4 (br, 1H, NH); 11.5 (br, 1H, NH)

Table. (continued)

Product	Yield (%)/ Method	mp (°C)[a] (solvent)	Molecular Formula[b]	MS (70 eV)[c] *m/z* (%)	^{1}H-NMR (DMSO-d_6/TMS)[d] δ, *J* (Hz)
5e	60/A	245–248 (EtOH)	$C_{22}H_{23}ClN_6O_3S$ (486.9)	450 (M^+ – HCl, 8); 433 (69), 406 (31), 393 (100); 260 (43), 151 (36), 134 (21), 44 (90)	[e]2.07 (m, 2H, $CH_2CH_2CH_2$); 2.5 (s, 3H, NCH_3); 2.87 (m, 4H, CH_2N, CH_2C); 3.47 (s, 3H, OCH_3); 6.62 (d, 2H, J = 9, C_6H_4); 7.15 (br, 1H, NH); 7.38 (d, 2H, J = 6, C_6H_4); 7.49 (d, 2H, J = 6, C_6H_4); 7.97 (d, 2H, J = 9, C_6H_4); 8.3 (s, 1H, CH)
5f	82/B	191–193 (MeOH)	$C_{21}H_{23}BrN_2O_2S$ (447.4)	366 (M^+ – HBr, 8), 322 (8), 308 (50), 280 (15), 151 (18), 134 (14), 105 (71), 82 (14), 77 (61), 44 (100)	
5g[j]	78/B	208–209 (MeOH)	$C_{21}H_{22}Br_2N_2O_2S$ (526.3)	386 (20), 183 (30), 155 (23), 151 (24), 80 (12), 58 (22), 44 (100)	2.06 (m, 2H, $CH_2CH_2CH_2$); 2.5 (s, 3H, NCH_3); 3.0 (m, 4H, CH_2N, CH_2C); 3.81 (s, 3H, OCH_3); 7.01 (d, 2H, J = 9, C_6H_4); 7.75 (s, 4H, C_6H_4); 7.8 (d, 2H, J = 9, C_6H_4)
5h[k]	86/A	220–222 (MeCN)	$C_{15}H_{18}ClN_3OS$ (323.8)	287 (M^+ – HCl, 5), 243 (19), 230 (100), 134 (22), 83 (40), 70 (13), 44 (68)	[i]2.12 (m, 2H, $CH_2CH_2CH_2$); 2.56 (s, 3H, NCH_3); 3.0 (m, 4H, NCH_2, CH_2C); 3.56 (s, 3H, OCH_3); 6.75 (d, 2H, J = 9, C_6H_4); 7.62 (d, 2H, J = 9, C_6H_4)
5i[l]	74/A	182–183 (MeCN)	$C_{24}H_{23}BrN_4OS$ (495.4)	414 (M^+ – HBr, 27), 371 (48), 357 (63), 349 (48), 151 (38), 82 (50), 80 (57), 44 (100), 41 (65)	[h]2.3 (m, 4H, CH_2, CH_2); 2.3 (s, 3H, NCH_3); 2.95 (m, 2H, CH_2); 3.75 (s, 3H, OCH_3); 6.87 (d, 2H, J = 9, C_6H_4); 7.43 (s, 5H, C_6H_5); 7.81 (d, 2H, J = 9, C_6H_4)
5j	87/B	204–205 (EtOH)	$C_{23}H_{26}Br_2N_2O_2S$ (554.4)	473 (M^+ – HBr, 2), 388 (8), 289 (25), 185 (20), 183 (22), 157 (13), 155 (14), 84 (28), 71 (10), 58 (100), 44 (14)	1.2 (t, 3H, CH_3); 1.7 (m, 4H, CH_2CH_2); 2.95 (m, 6H, CH_2, CH_2N, CH_2N); 3.8 (s, 3H, OCH_3); 7.1 (d, 2H, J = 8, C_6H_4); 7.8 (s, 4H, C_6H_4); 8.0 (d, 2H, J = 8, C_6H_4)
5k	51/A[m]	155–157 (EtOH)	$C_{16}H_{23}BrN_4O_2S$ (415.4)	334 (M^+ – HBr, 11), 317 (23), 300 (26), 276 (44), 263 (56), 146 (24), 115 (19), 102 (15), 30 (100)	1.37 (t, 3H, CH_3); 1.6–1.9 (m, 6H, CH_2, CH_2CH_2); 2.75 (m, 4H, CH_2, CH_2); 3.5 (m, 2H, NCH_2); 7.71 (d, 2H, J = 9, C_6H_4); 8.3 (d, 2H, J = 9, C_6H_4); 7.89 (br, 3H, NH_2, NH)
5l	78/A	220–222 (MeCN/ DMF)	$C_{21}H_{25}BrN_4O_2S$ (477.4)	396 (M^+ – HBr, 1); 348 (2), 311 (4), 146 (3), 115 (5), 44 (100)	
6a	40/A	70–71 (C_6H_6)	$C_6H_{13}N_3S$ (195.3)		[h]2.06 (m, 2H, $CH_2CH_2CH_2$); 2.25 (s, 3H, CH_3C); 2.87 (m, 2H, CH_2); 3.00 (s, 3H, NCH_3); 3.37 (t, 2H, CH_2); 4.00 (s, 1H, CH)
6b	65/A[n] 58/A[o]	111–112 (EtOH)	$C_{14}H_{15}N_3S$ (257.4)		[i]2.15 (m, 2H, $CH_2CH_2CH_2$); 3.15 (s, 3H, NCH_3); 3.15 (m, 2H, CH_2); 3.75 (t, 2H, CH_2); 7.12 (s, 5H, C_6H_5); 7.20 (s, 1H, CH)
6c	75/A	143–144 (EtOH)	$C_{14}H_{14}BrN_3S$ (336.3)		[h]2.06 (m, 2H, $CH_2CH_2CH_2$); 3.0 (s, 3H, CH_3); 3.0 (m, 2H, CH_2); 3.43 (t, 2H, CH_2); 7.12 (s, 1H, CH); 7.56 (d, 2H, C_6H_4); 7.87 (d, 1H, C_6H_4)
6d	62/A	145–147 (MeCN/ MeOH)	$C_{14}H_{14}N_4O_2S$ (302.3)		[h]2.12 (m, 2H, $CH_2CH_2CH_2$); 3.0 (s, 3H, CH_3); 3.0 (m, 2H, CH_2); 3.43 (t, 2H, CH_2); 7.18 (s, 1H, CH); 7.9 (d, 2H, C_6H_4); 8.25 (d, 2H, C_6H_4)
7	79/A	323–325 (MeOH)	$C_{20}H_{20}Br_2N_3S$ (494.3)	413 (M^+ – Br, 100), 411 (100), 412 (50), 383 (10), 294 (11), 198 (8), 77 (8)	2.1 (m, 2H, $CH_2CH_2CH_2$); 3.05 (s, 3H, CH_3); 3.05 (m, 2H, CH_2); 3.45 (t, 2H, CH_2); 7.9–8.2 (m, 10H, C_6H_4, C_6H_5, CH)

[a] Uncorrected, measured with a heating block Boetius.
[b] Satisfactory microanalyses: C ±0.34 (except for **5d**: +0.41), H ±0.24, N ±0.25 (except for **5j**: +0.3), S ±0.27.
[c] Recorded on a Hewlett-Packard HP 5995A spectrometer.
[d] Obtained on a Tesla BS 587 (80 MHz) NMR spectrometer.
[e] The intermediate **3a**, 2-[amino(4-nitrobenzylthio)methylenamino]-1-methyl-4,5-dihydro-3*H*-pyrrolium bromide, was obtained by refluxing a 1:1 mixture of the respective compounds **1** and **2** in MeOH without added base for 1 h; yield: 92%; mp 93–106 °C (dec) (MeCN).
^{1}H-NMR (DMSO-d_6/TMS): δ = 2.0 (m, 2H, $CH_2CH_2CH_2$); 2.6 (t, 2H, J = 6 Hz, CH_2); 3.0 (s, 3H, CH_3); 3.61 (t, 2H, J = 6 Hz, CH_2); 4.29 (s, 2H, CH_2); 7.5 (d, 2H, J = 8 Hz, C_6H_4); 8.02 (d, 2H, J = 8 Hz, C_6H_4); 9.3 (br, 1H, NH).
[f] The free base of **5b** was obtained by heating the hydrobromide **5b** (4.5 g) in MeOH (25 mL) containing a concentrated aqueous solution of K_2CO_3 (2.1 g) for 5 min, and evaporating the solvent; yield: 61%; mp 137–139 °C (MeCN).
MS: *m/z* = 368 (71), 311 (100), 278 (11), 77 (29), 44 (64).
[g] ^{13}C-NMR (DMSO-d_6/TMS): δ = 23.4, 27.9, 32.3, 47.6, 119.2, 124.7, 129.3, 138.6, 159.6, 164.3, 234.9 (Recorded on a Bruker WM-300 spectrometer).
[h] In $CDCl_3$.
[i] In CF_3CO_2H.
[j] IR (KBr): ν_{CO} = 1640 cm^{-1} (Recorded on a Specord IR 72 Spectrophotometer).
UV (MeOH): λ_{max} (log ε) = 229 (4.14); 269 (4.18); 353 (4.32) nm. (Recorded on a UV-Vis Specord spectrometer (Carl Zeiss Jena).
[k] IR (KBr): ν_{CN} = 2210 cm^{-1}.
[l] IR (KBr): ν_{CN} = 2210 cm^{-1}.
[m] The starting material **1** was used without previous purification.
[n] The starting material **2** was phenacyl bromide.
[o] The starting material **2** was (2-bromo-1-phenylethylidene)malononitrile.



6	R^3 in 3	R^4 in R^3	R^4 in 6
a	CH_3CO	CH_3	CH_3
b	PhCO	Ph	Ph
		Ph	Ph
c	$4\text{-}BrC_6H_4CO$	$4\text{-}BrC_6H_4$	$4\text{-}BrC_6H_4$
d	$4\text{-}NO_2C_6H_4CO$	$4\text{-}NO_2C_6H_4$	$4\text{-}NO_2C_6H_4$

The 4-(ω-aminoalkyl)thiazole salts **5** are stable crystalline compounds. Depending on the substituents R^2 and R^3, their color ranges from colorless to orange. The free bases of **5** can be generated by treatment of the hydrohalides **5** with potassium carbonate in methanol (see footnote f in the Table; **5b**). The structure of the 4-(ω-aminoalkyl)thiazole hydrohalides **5** was proven by microanalysis and spectrometric data, in particular, by ^{1}H-NMR data. The following order of chemical shifts δ of the methylene proton signals and of the signals of the alkyl substituent R^1, which is also typical of other ω-aminoalkylazoles, is observed in the ^{1}H-NMR spectra: $CH_2\underline{CH_2})_nCH_2 < NR < CH_2{-}N \approx CH_2$-thiazole. This order differs considerably from the order found for compounds having intact lactam rings[3] such as **1** or **3**: $CH_2(\underline{CH_2})_nCH_2 < CH_2{-}C{=}N < CH_2N < R^1N$. The spiro isomers **4** would show still other chemical shifts δ.[16, 17] Further, ω-aminoalkyl chains such as in **5** exhibit typical fragmentation patterns in their mass spectra in which *m/z* fragments of $R^1NH{=}CH_2$ and $R^1NHCHCH_2$ are found; these fragments could have arisen from α-cleavage or McLafferty rearrangement, respectively.

The synthesis of 4-(ω-aminoalkyl)thiazoles **5** described here is satisfactorily compatible with a variety of substituents R^1, R^2, and R^3 (see Table). However, the substituent R^3 has to be sufficiently electron-withdrawing in order to enable deprotonation and cyclization of the primary *S*-alkylation products **3**. For example, the reaction of compounds **1** with methyl iodide yields the *S*-methyl compounds **3** (R^3 = H)[1] without problems. However, compounds **3** resist further transformation to **5** under the conditions used successfully in the cases mentioned above.

When the semicyclic thiourea derivatives **1** (R^2 = NH_2 or NH–Ar) are submitted to the reaction with α-haloketones **2** (R^3 = COR^4) or the (2-bromo-1-phenylethyliden)malononitrile [**2**, R^3 = C(Ph)=C(CN)$_2$, X = Br], ring transformation products **5** are not obtained, the isolated products being 2-(1-methylpyrolidin-2-ylidenamino)thiazole derivatives **6** or **7**. Products **6** and **7** (see Table) are derived from a Hantzsch-type thiazole synthesis, i.e., they are formed via *S*-alkylation to **3** and subsequent attack of the amino group R^2 at the carbonyl C-atom (R^3 = COR^4), the α-haloketones **2** (R^3 = COR^4) acting as C–C synthons.

The synthesis of 4-(ω-aminoalkyl)thiazoles **5** from **1** and **2** represents an interesting type of ring transformation in which a lactam ring of the substrate is opened while a heteroaromatic ring is formed. Such ring transformations have rarely been investigated (see the references cited in Lit.[3, 15]). It is worthy of note that in a recently published reaction[16] of semicyclic 3-amino-2-alkenylthiones (C-analogs of **1**) with α-haloketones, ring-fused thiophenes such as tetrahydrothienoazepines were obtained instead of ring transformation products (ω-aminoalkylthiophenes). The ring-fused thiophenes arise from intramolecular condensation of the carbonyl group with the ω-amino substituent in the intermediately formed thiophene analogs of **5**.

4-(ω-Aminoalkyl)thiazole Hydrohalides 5 and 2-(1-Methylpyrrolidin-2-ylidenamino)thiazole Derivatives 6 and 7; General Procedures:

Method A: The substituted methyl halide **2** (0.01 mol) is added to a mixture of the semicyclic *N'*-(aminothiocarbonyl)amidine **1** (R^2 = NH_2 or NHR) or *N'*-(thioacyl)amidine **1** (R^2 = COAr)[1, 13] (0.01 mol) and MeCN (20 mL). The mixture is briefly heated to boiling, then cooled slightly, Et_3N (2 g, 0.02 mol) is added, and refluxing is continued for 30 min. When the solution has cooled to room temperature the product crystallizes or is precipitated by the addition of a few drops of water. It is isolated by suction and recrystallized.

Method B: A mixture of the semicyclic *N'*-(thioacyl)amidine **1f, g, j** (0.01 mol), the substituted methyl halide **2** (0.01 mol), 1,2-dimethoxyethane (25 mL), and Et_3N (1 g, 0.01 mol) is stirred for 1 h at r.t. The precipitated product is isolated by suction and recrystallised.

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