Ring-Chain-Transformations [1]: Synthesis of ω-Functionalized Alkylthio-1,2,4-triazoles by Reaction of Cyclic *S*-Analogous *N*-Cyano or *N*-Aroylcarbonimidoesters with Hydrazines

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Received November 20, 1991

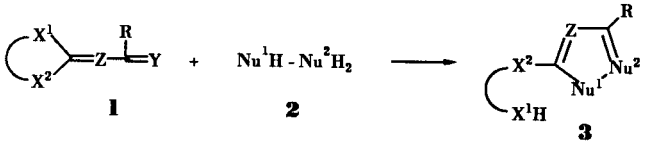
Cyclic *N*-cyanocarbonimidodithioesters **4** or *N*-aroylcarbonimidothioic acid esters **10** react regioselectively with arylhydrazines and methylhydrazine by a ring chain transformation reaction forming ω-functionalized 3-alkylthio-1,2,4-triazoles **8** and **11** or 5-alkylthio-1,2,4-triazoles **9**.

J. Heterocyclic Chem., **29**, 1209 (1992).

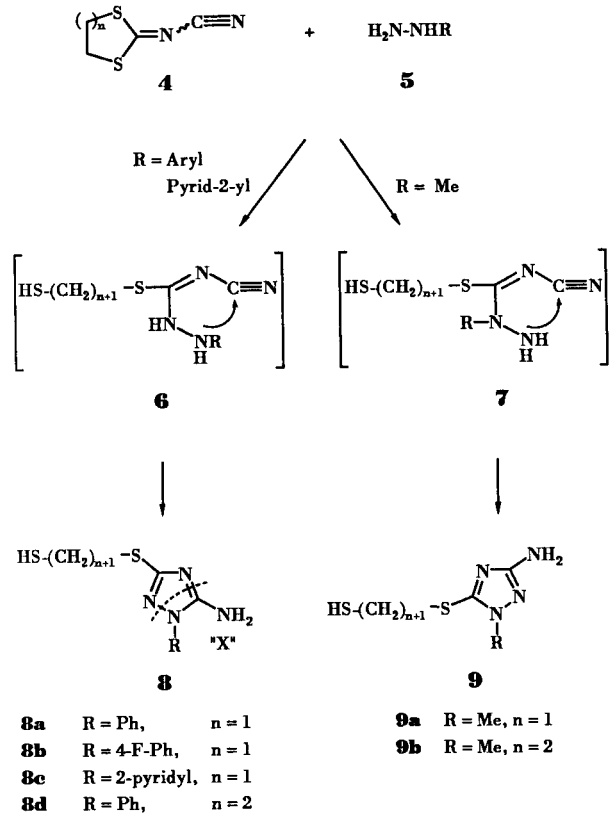
Recently we developed a useful concept of synthesizing ω-functionalized alkylheteroaromatics **3** by ring chain trans-formation of bridged 1,3-dicarbonyl heteroanalogous **1** (X^2 = CH_2, NH) [2,3,4,5]. Reaction of the latter with binucleophiles **2** at the two electrophilic sites causes both, formation of a heteroaromatic system and opening of the starting saturated ring thus affording the ω-functionalized alkyl chain. For example, 3-anilino-5-(2-thioethylamino)-1,2,4-triazole **3** (Z = Nu^2 = N, Nu^1 = X^2 = NH, X^1 = S, R = NHC_6H_5) could be synthesized starting from a semicyclic thiourea derivative **1** (X^1 = S, X^2 = NH, Z = N, Y = S, R = NHC_6H_5) and hydrazine **2** (Nu^1 = NH, Nu^2 = N) [2].

We report now on the possibility to extend this synthetic principle to the synthesis of ω-functionalized alkylthiotriazoles, whose alkyl group is separated from the heterocyclic ring by a sulfur atom (X^2 = S). Cyclic *N*-cyanocarbonimidodithioesters **4** (n = 1, 2) [6] were chosen as appropriate starting materials for the synthesis of ω-thioalkylthio-1,2,4-triazoles. The intensively investigated nonbridged *N*-cyanocarbonimido-*S,S*-dialkyldithioesters are known to afford 3-amino-5-alkylthio-1,2,4-triazoles or their 5-amino-3-alkylthio-isomers in reactions with hydrazines [7,8]. Heating of solutions of bridged *N*-cyanocarbonimidodithioic esters **4** and arylhydrazines or 2-pyridylhydrazine **5** (R = aryl, 2-pyridyl) gave 5-amino-3-(ω-thioalkylthio)-1,2,4-triazoles **8** in high yields. These novel colorless crystalline compounds show NH-absorptions rather than C≡N-signals in the ir. The fragmentation of the thioalkylthio substituent according to an α- and β-cleavage as well as to a McLafferty rearrangement dominate in the ms spectra. Alternative isomeric 3-amino-5-thioalkylthio-1,2,4-triazole structures **9** can be ruled out by the fact that intensive fragment peaks M^+-X (see **8**) appear in the ms spectra. Final proof is given by ^{13}C-nmr spectroscopy. Reiter *et al.* [9] found that the chemical shifts of the two triazole carbon atoms of 3-alkylthio-5-amino-1,2,4-triazoles show differences of 0.3-3.0 ppm. The ^{13}C-nmr δ-values of the 5-alkylthio-3-amino isomers however differed by 12-15 ppm and were not influenced by the type of alkyl and *N*-substi-

Scheme 1



Scheme 2



8a R = Ph, n = 1
8b R = 4-F-Ph, n = 1
8c R = 2-pyridyl, n = 1
8d R = Ph, n = 2

9a R = Me, n = 1
9b R = Me, n = 2

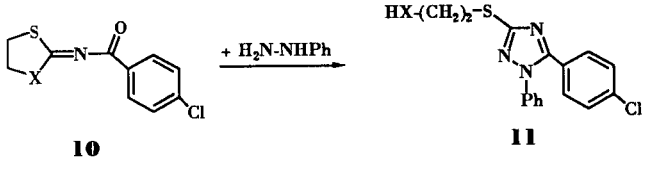
tuents [8,9]. All compounds obtained from **4** and aryl or 2-pyridylhydrazine show shift differences $\Delta\delta$ of the heterocyclic carbon atoms of around 3 ppm thus providing evidence for structure **8**.

In contrast, reactions of *N*-cyanocarbonimidodithioic esters **4** with methylhydrazine **5** (R = Me) at room temperature give the 3-amino-5-thioalkylthio-1,2,4-triazole isomers **9**. Shift differences, $\Delta\delta$ of 16 ppm clearly demonstrate the proposed structure.

All products **8** and **9** obtained from the reaction of **4** with hydrazines **5** can be explained to be formed by the same mechanism. The more nucleophilic N-atom (NH_2 in case of R = aryl, hetaryl; $NHCH_3$ in case of R = CH_3) of the corresponding hydrazine **5** primarily attacks the imido carbon atom. The isothiosemicarbazide intermediates **6** and **7** thus formed undergo intramolecular cyclization by addition of the NH-group of the hydrazine **5** N-atom to the cyano group. A similar dependence of the regioisomerism of triazole formation on the substituents attached to the hydrazines was found by Reiter *et al.* [9] in corresponding reactions in the non-bridged *N*-cyanocarbonimido-*S,S*-dialkyldithioester series.

Extending the general Scheme 1 to bridged 1,3-dicarbonylheteroanalogs **1**, having a carbonyl group (Y = O) or another heteroatom than S in the saturated starting ring (X^1 or $X^2 \neq S$), we investigated reactions of 2-(4-chlorobenzoylimino)dithiolane **10** (X = S) [10] and 3-phenyl-1,3-thiazolidine **10** (X = NC_6H_5) [11] with phenylhydrazine. In both cases ω-functionalized 3-alkylthio-1,5-diaryl-1,2,4-triazoles **11** were isolated. Alternative isomeric 5-alkylthio-1,3-diaryl-1,2,4-triazole structures can be excluded, since no down field shift of the *ortho* aryl protons is found, as it is known for 1,3-diaryl-1,2,4-triazoles, when both aryl substituents are in the same plane [2,12]. Furthermore the 3-(2-anilinoethylthio)-1,2,4-triazole **11b** (X = NPh) exhibits characteristic fragments derived from onium cleavage (m/z = 106, elimination of $PhNHCH_2^+$) and McLafferty rearrangement (m/z = 287, M^+ -$PhNHCH{=}CH_2$). Hence, 3-(*N*-phenyl-*N*-thioethyl)amino-1-phenyl-5-(4-chlorophenyl)-1,2,4-triazole as an isomeric structure derived from the more probable cleavage of the C-S bond of **10** (X = NC_6H_5) also can be ruled out. Hitherto such a preferred cleavage of the C-N rather than a C-S bond in 2-cyanocarbonimino-1,3-thiazolidine was only found if very strongly electron withdrawing substituents (COR or SO_2R) are attached at the 3-position [13].

Scheme 3



10 **11**

10a, 11a X = S
10b, 11b X = NPh

The foregoing results demonstrate the successful extension of the concept of ring transformation by ring chain transfer to the synthesis of ω-functionalized alkylthiotriazoles. After finishing our investigations [5] further examples were reported by Iwata *et al.* [13] giving ω-sulfonylaminoalkylthio- and acylamino-alkylthio-1,2,4-triazoles in reactions of the corresponding 2-cyanocarbonimino-1,3-thiazolidines with hydrazine hydrate.

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-spectrometer. The ^{13}C-nmr spectra were recorded on a Bruker AC 300. Mass spectra were taken with a Hewlett Packard 599 SA spectrometer.

5-Amino-3-(ω-mercaptoalkylthio)-1,2,4-triazoles **8**.

General Procedure.

A mixture of **4** (0.01 mole) and arylhydrazine **5** (R = aryl) (0.01 mole) in 20 ml ethanol was refluxed for 1 hour. After evaporation of some solvent and cooling the resulting precipitate was filtered by suction and recrystallized.

5-Amino-3-(2-mercaptoethylthio)-1-phenyl-1,2,4-triazole **8a** (R = Ph, n = 1).

This compound had mp 153-154° (acetonitrile), yield 68%; ms: (m/z) 252 (M^+, 6), 192 (100), 119 (45), 108 (17), 77 (99); ^{1}H-nmr (DMSO-d_6): δ 2.71 (m, 2H, SCH_2), 3.11 (m, 2H, SCH_2), 6.52 (s, 2H, NH_2), 7.29 (s, 5H, Ph); ^{13}C-nmr (DMSO-d_6): δ 24.6, 34.6, 127.1, 129.4, 137.0, 155.5, 157.0.

Anal. Calcd. for $C_{10}H_{12}N_4S_2$ (252.35): C, 47.59; H, 4.79; N, 22.20; S, 25.41. Found: C, 47.82; H, 4.63; N, 22.46; S, 25.18.

5-Amino-1-(4-fluorophenyl)-3-(2-mercaptoethylthio)-1,2,4-triazole **8b** (R = 4-F-Ph, n = 1).

This compound had mp 114-116° (ethanol), yield 73%; ms: (m/z) 270 (M^+, 7), 210 (100), 137 (35), 123 (16), 95 (78); ^{1}H-nmr (DMSO-d_6): δ 3.18 (t, J = 8 Hz, 2H, SCH_2), 3.53 (t, J = 8 Hz, 2H, SCH_2), 6.56 (s, 2H, NH_2), 7.49 (s, 4H, Ph); ^{13}C-nmr (DMSO-d_6): δ 34.0, 36.5, 116.4, 125.5, 155.5, 156.9, 159.3, 162.5.

Anal. Calcd. for $C_{10}H_{11}FN_4S_2$ (270.35): C, 44.43; H, 4.10; N, 20.72; S, 23.72. Found: C, 44.56; H, 4.17; N, 20.68; S, 23.69.

5-Amino-3-(2-mercaptoethylthio)-1-(2-pyridyl)-1,2,4-triazole **8c** (R = 2-pyridyl, n = 1).

This compound had mp 120-122° (acetonitrile), yield 75%; ms: (m/z) 253 (M^+, 10), 220 (29), 193 (100), 78 (51), 66 (10); ^{1}H-nmr (DMSO-d_6): δ 2.96 (m, 2H, SCH_2), 3.20 (m, 2H, SCH_2), 3.61 (s, 2H, NH_2), 7.18 (d, J = 5 Hz, 1H), 7.81 (m, 2H), 8.4 (d, J = 5 Hz, 1H); ^{13}C-nmr (DMSO-d_6): δ 24.8, 35.2, 112.8, 120.0, 138.9, 146.7, 151.7, 156.0, 158.1.

Anal. Calcd. for $C_9H_{11}N_5S_2$ (253.34): C, 42.68; H, 4.34; N, 27.66; S, 25.29. Found: C, 42.38; H, 4.33; N, 28.06; S, 24.84.

5-Amino-3-(3-mercaptopropylthio)-1-phenyl-1,2,4-triazole **8d** (R = Ph, n = 2).

This compound had mp 84-86° (ethyl acetate), yield 82%, ms: (m/z) 266 (M^+, 9), 206 (30), 119 (44), 107 (18), 77 (100); ^{1}H-nmr (300 MHz, DMSO-d_6): δ 1.4 (t, J = 7 Hz, 1H, SH); 2.04 (p, J = 7 Hz, 2H, CH_2), 2.67 (q, J = 7 Hz, 2H, SCH_2), 3.20 (t, J = 7 Hz, 2H, SCH_2), 5.13 (s, 2H, NH_2), 7.59 (m, 5H, Ph); ^{13}C-nmr (DMSO-d_6): δ 23.3, 30.1, 33.4, 123.1, 127.9, 129.8, 136.6, 154.6, 157.5.

Anal. Calcd. for $C_{11}H_{14}N_4S_2$ (266.38): C, 49.62; H, 5.26; N, 21.05; S, 24.02. Found: C, 49.41; H, 5.20; N, 20.90; S, 23.90.

3-Amino-5-(ω-mercaptoalkylthio)-1,2,4-triazoles **9**.

General Procedure.

A solution of methylhydrazine **5** (R = Me) (0.46 g, 0.01 mole) in 10 ml of ethanol was added dropwise with stirring to a suspension of 0.01 mole of cyclic dithioic acid ester **4** in 20 ml of ethanol. After 2 hours the precipitate was filtered by suction and recrystallized.

3-Amino-1-methyl-5-(2-mercaptoethylthio)-1,2,4-triazole **9a** (n = 1).

This compound had mp 208-210° (ethyl acetate), yield 78%; ms: (m/z) 190 (M^+, 5), 157 (30), 130 (100), 87 (46), 43 (61); ^{1}H-nmr (DMSO-d_6): δ 3.31 (m, 4H, $(CH_2)_2$), 3.44 (s, 3H, NMe), 5.75 (s, 2H, NH_2); ^{13}C-nmr (DMSO-d_6): δ 33.2, 34.6, 34.6, 147.7, 163.4.

Anal. Calcd. for $C_5H_{10}N_4S_2$ (190.28): C, 31.57; H, 5.26; N, 29.47; S, 33.68. Found: C, 31.83; H, 5.10; N, 29.50; S, 33.55.

3-Amino-1-methyl-5-(3-mercaptopropylthio)-1,2,4-triazole *9b* (n = 2).

This compound had mp 143-145° (ethyl acetate), yield 78%; ms: (m/z) 204 (M^+, 20), 157 (39), 144 (50), 130 (100), 99 (91), 43 (70); ^{1}H-nmr (DMSO-d_6): δ 2.46 (m, 2H, CH_2); 3.95 (m, 4H, $(CH_2)_2$), 4.19 (s, 3H, Me), 6.86 (s, 2H, NH_2); ^{13}C-nmr (DMSO-d_6): δ 29.2, 31.3, 34.2, 34.4, 147.8, 163.1.

Anal. Calcd. for $C_6H_{12}N_4S_2$ (204.31): C, 35.26; H, 5.92; N, 27.42. Found: C, 35.53; H, 5.66; N, 27.50.

5-(4-Chlorophenyl)-3-(2-mercaptoethylthio)-1-phenyl-1,2,4-triazole **11a** (X = S).

To a refluxing solution of **10a** (X = S) (0.01 mole) in 20 ml of ethanol was dropped phenylhydrazine **5** (R = Ph) (0.01 mole). After 1 hour the reaction mixture was cooled and the precipitate filtered by suction. Recrystallization gave 1.95 g (79%) of **11a**, mp 81-83° (ethanol); ms: (m/z) 347 (M^+, 3), 314 (23), 287 (41), 150 (31), 77 (100), 43 (80); ^{1}H-nmr (DMSO-d_6): δ 3.37 (m, 4H, $(CH_2)_2$), 7.55 (m, 9H).

Anal. Calcd. for $C_{16}H_{14}ClN_3S_2$ (347.89): C, 55.24; H, 4.06; N, 12.08. Found: C, 55.41; H, 4.26; N, 12.35.

3-Anilinoethylthio-5-(4-chlorophenyl)-1-phenyl-1,2,4-triazole **11b** (X = NPh).

A mixture of **10b** (3.16 g, 0.01 mole) and phenylhydrazine **5** (R = Ph) (1.68 g, 0.01 mole) in 20 ml of glacial acetic acid was refluxed for 4 hours. After cooling 100 ml ice water was added. The precipitate was filtered by suction and purified by flash chromatography, eluting with chloroform:methanol (95:5) to give 2.91 g (73%) of **11b**. This compound had mp 125-127°; ms: (m/z) 406 (M^+, 3), 300 (5), 287 (20), 214 (15), 106 (59), 92 (13), 119 (75), 77 (100); ^{1}H-nmr (DMSO-d_6): δ 3.4 (t, J = 7.5 Hz, 2H, SCH_2); 4.1 (t, J = 7.5 Hz, 2H, NCH_2), 7.3 (m, 4H), 7.4 (m, 8H), 8.05 (d, J = 9 Hz, 2H); ^{13}C-nmr (DMSO-d_6): δ 27.1, 52.3, 125.0, 126.6, 128.2, 128.9, 131.1, 134.9, 138.1, 140.2, 171.6, 175.0.

Anal. Calcd. for $C_{22}H_{19}ClN_4S$ (406.94): C, 64.93; H, 4.71; N, 13.77. S, 7.88. Found: C, 64.99; H, 4.79; N, 13.77; S, 7.87.

Acknowledgements.

We thank the Fonds der Chemischen Industrie for financial support and the Schering AG for recording nmr-spectra.

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