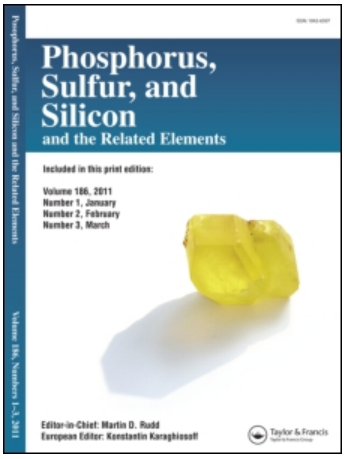

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SYNTHESES OF S,N-HETEROCYCLES FROM N-THIOACYLLACTAMIMINES

J. Bohrisch[a]; M. Pätzel[a]; L. Grubert[a]; J. Liebscher[a]
[a] Institut für Organische und Bioorganische Chemie, Humboldt-Universität, Berlin, Germany

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Communication

SYNTHESES OF S,N-HETEROCYCLES FROM N-THIOACYLLACTAMIMINES

J. BOHRISCH, M. PÄTZEL, L. GRUBERT and J. LIEBSCHER*
Institut für Organische und Bioorganische Chemie, Humboldt-Universität, Hessische Str. 1-2, 10115 Berlin, Germany

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Nitrile imines undergo cycloadditions to the thiocarbonyl group of N-thioacyllactamimines **1** giving 1,3,4-thiadiazolines **2**. Depending on the substituents oxidation of N-thioacyllactamimines **1** leads to different products, such as condensed 5-amino-1,2,4-thiadiazolium bromides **5**, 3,5-diaryl-1,2,4-dithiazolium salts **6**, 3,5-diaryl-1,2,4-thiadiazoles **7** or 2-benzothiazolyliminopyrrolidine **8**.

Key words: N-Thioacyllactamimines; 2,3-dihydro-1,3,4-thiadiazoles; condensed 5-amino-1,2,4-thiadiazolium salts; 2-amidino-benzothiazoles; 1,2,4-dithiazolium salts; oxidation; cycloaddition.

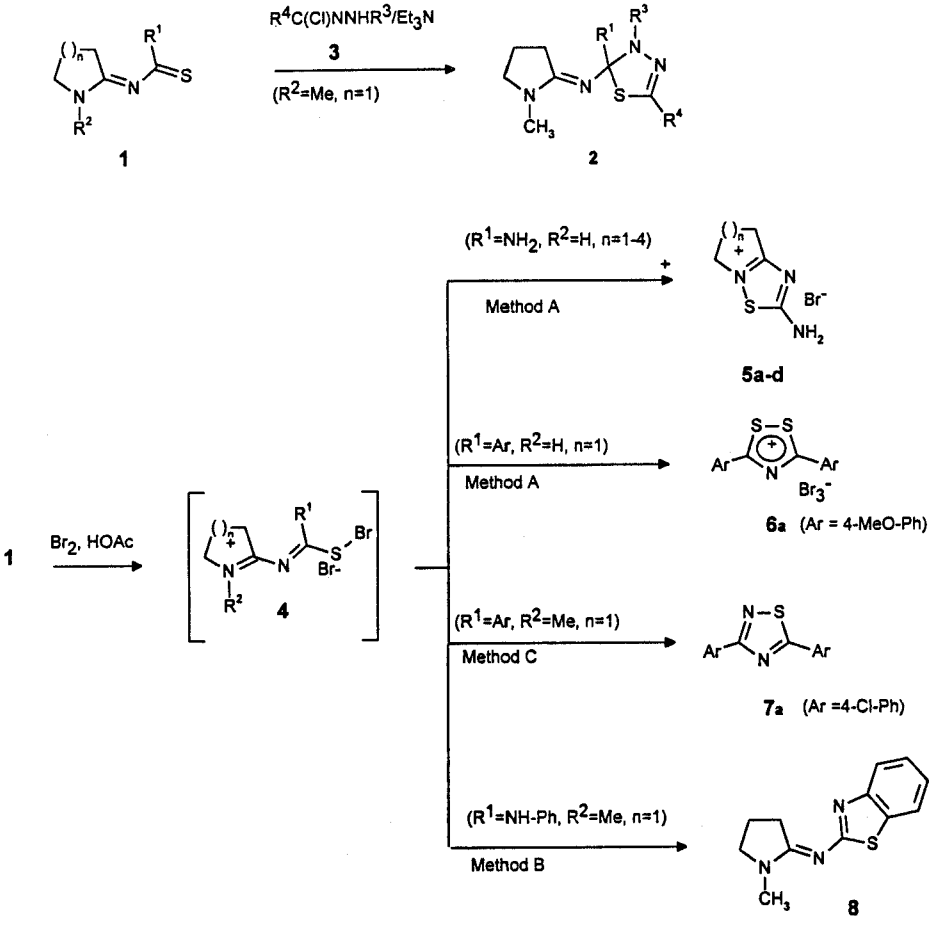
N-Thioacyllactamimines **1** can easily be prepared by condensation of activated lactam derivatives, e.g. lactam acetals or lactim ethers with thioureas or thioamides.[1,3] These compounds are proved to be very potent starting materials for the synthesis of aminoalkyl-heterocycles according to a new concept of ring chain transformation. In this respect they give, for example, 3-aminoalkyl-1,2,4-thiadiazoles[2] (C—N—C—S-building block) or 3-aminoalkyl-1,2,4-triazoles[3] (C—N—C-building block). Furthermore they react with 1,4-binucleophiles as C_1-synthon.[4]

While further exploring the synthetic potential of **1** we were interested to apply them to the synthesis of S,N-heterocycles by reaction with nitrile imines or by oxidation. Practical investigations revealed that reactions of compounds **1** with nitrile imines, generated in situ from hydrazinoyl chlorides **3**, afford 1:1 cycloadducts. Their analysis especially by ^{13}C-NMR and mass spectroscopy showed that 2,3-dihydro-1,3,4-thiadiazoles **2** were formed (addition to C=S), rather than triazoles, which could be derived from the addition of the nitrile imine to the C—N double bond of **1**. Compared with the starting compounds **1** the typical signal of the amidine-C-atom around 170 ppm survived in the products **2**, while the signal of the thiocarbonyl group was lost. Additional evidence for the assigned structure **2** came from the mass spectra, where a characteristic elimination of a R^1-S fragment was found. This kind of fragmentation corresponds with the known behaviour of 2,3-dihydro-1,3,4-thiadiazoles under the conditions of mass spectroscopy and is caused by ring opening and rearrangement.[5]

We further investigated the reactions of N-thioacyllactamimines **1** with oxidising reagents. In analogy to known reactions of thiocarbonyl moieties with bromine[6] a primary attack of the oxidising reagent at the sulphur atom had to be expected, giving intermediates **4**. Since the N-thioacyllactamimine **1** represents a polyfunctional system (nucleophilic properties not only at the sulphur atom but also at the

two nitrogen atoms and eventually at the substituent R^1) various possibilities for the subsequent cyclisation of the intermediate **4** had to be taken into consideration.

Reacting the thiourea derivatives **1** ($R^1 = NH_2$, $R^2 = H$) with bromine bicyclic 5-amino-1,2,4-thiadiazolium salts **5** were isolated in nearly quantitative yield. Obviously the intermediate sulfenylbromide **4** is stabilized through oxidative S—N bond formation. A similar reaction behaviour is known from thioacylketene aminals[7,11] and N-imidoylthioureas.[8] The hitherto unknown compounds **5** are stable crystalline substances. The appearance of two signals for the NH_2-group in the ^{1}H-NMR spectra of compounds **5** at $\delta_1 \approx 9.5$ ppm and $\delta_2 \approx 9.9$ ppm could be caused by hindered rotation around the exocyclic C—N bond.



	R^1	R^3	R^4
2a	4-MeO-Ph	Ph	Ph
2b	4-MeO-Ph	3-Cl-Ph	COOEt
2c	4-MeO-Ph	Ph	COOEt

5	**a**	**b**	**c**	**d**
n	1	2	3	4

Although the structural feature (R^2 = H in **1**) for oxidative S—N bond formation was found in aryl substituted N-thioacyllactamimines **1** (R^1 = Aryl, R^2 = H) too, these reactants on treatment with bromine gave no 1,2,4-thiadiazoles analogous to **5** but either 3,5-diaryl-1,2,4-dithiazolium salts **6** or 3,5-diaryl-1,2,4-thiadiazoles **7**. An analogous transformation to dithiazolium salts **6** had been found with N-thioaroylamidines and was explained by S—S bond connection and subsequent elimination of the imidoyl moieties or sulphur, respectively.[9]

Finally the phenylthiourea derivative **1** (R^1 = NHPh, R^2 = Me) was submitted to oxidation with bromine. Since the nitrogen atom of the pyrrolidine ring is substituted no intramolecular S—N bond connection was possible. Instead an oxidative C—S bond formation to the benzothiazole **8a** (isolated as hydroperchlorate) was observed. Similar cyclisations with simple N-arylthioureas are well known[11] and had first been observed by Huggershoff.[10]

EXPERIMENTAL

2,3-Dihydro-1,3,4-thiadiazoles **2**. To a solution of 10 mmol N-thioacyllactamimine **1** in 20 ml benzene 10 mmol hydrazinoyl acid chlorides **3** and 12 mmol triethylamine were added. After 1 h of reflux the solvent was evaporated and 20 ml aqueous ethanol were added. The precipitate was filtered by suction and recrystallised.

TABLE I

5-Amino-1,2,4-thiadiazolium bromides **5a-c**, 3,5-Diaryl-1,2,4-dithiazolium salt **6a**, 3,5-Diaryl-1,2,4-thiadiazole **7a** and 2-(benzothiazol-2-yl)imino-pyrrolidine **8** hydroperchlorate

Product[a]	yield (%)/ m.p.(°C)	MS (70 eV) m/e	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ, J(Hz)
2a	83 146 -147 (EtOH)	442 (M^+,1); 121(22); 55(100)	1.81 (m, 2H), 3.23 (m, 4H); 3.72(s, 3H); 6.90-7.76 (m, 14H)	19.3, 27.2, 31.3, 49.9, 55.1, 100.8, 113.5, 119.7, 125.7, 127.8, 128.4, 128.9, 129.2, 131.6, 138.6, 139.6, 141.6, 158.6, 166.7
2b	88 169 -171 (EtOH)	472 (M^+,3); 329(96); 215(23), 124(100)	1.31 (t, J=7Hz, 3H), 1.88 (br, 2H); 2.20 (br, 1H), 2.70 (br, 1H), 2.95(s, 3H); 3.22 (m, 2H), 3.71 (s, 3H), 4.31 (q, J=7Hz, 2H), 6.67-6.96 (m, 6H), 7.30 (m, 1H), 7.61 (m,1H)	14.2, 19.8, 27.5, 31.6, 50.5, 55.2, 62.1, 102.6, 113.5, 114.9, 117.0, 121.5, 127.9, 129.2, 132.4, 134.1, 139.1, 142.0, 159.2, 160.8, 167.4
2c	78 140 - 142 (EtOH)	438 (M^+,1); 329(16); 77(62), 29(100)	1.48 (t, J=7Hz, 3H), 1.89(br, 2H); 2.25(br, 1H), 2.65 (br, 1H), 3.03(s, 3H); 3.27 (m, 2H), 3.75 (s, 3H), 4.37 (q, J=7Hz, 2H), 6.70 (m, 3H), 7.05 (m, 2H), 7.25 (d, J=8, 2H), 7.75 (d, J=8Hz, 2H)	14.3, 18.9, 27.5, 31.6, 50.4, 55.2, 61.9, 102,8, 113.4, 117.1, 121.7, 128.0, 128.3, 139.6, 140.9, 159.1, 161.1, 167.4
5a	80/A 194-196 (AcOH)	141 (M^+-HBr, 15); 109(18); 80 (100); 41(43)	[b]2.49 (m, 2H), 2.96 (t, J=8Hz, 2H), 4.08 (t, J=8Hz, 2H), 9.50 (s, 1H), 9.91 (s,1H)	[b]23.5, 26.0, 50.1, 177.7, 185.1
5b	91/A 213 - 215 (AcOH)	155 (M^+-HBr, 100); 123(100); 80(75); 41(62)	[b]1.92 (m, 4H), 2.95 (t, J=7Hz, 2H), 4.02 (t, J=7Hz, 2H), 9.30 (s, 1H), 9.82 (s,1H)	
5c	74/A 181 - 184 (i-PrOH)	169 (M^+-HBr, 24); 137(100); 80 (82); 41(89)	[b]1.72 (m, 6H), 3.03 (t, J=7Hz, 2H), 4.20 (t, J=7Hz, 2H), 9.30 (s, 1H), 9.91 (s,1H)	
5d	78/A 194 - 196 (i-PrOH)	183 (M^+-HBr, 28); 151(20); 82 (56); 41(100)	[b]1.56 (m, 8H), 3.00 (t, J=7Hz, 2H), 4.30 (t, J=7Hz, 2H), 9.28 (s, 1H), 9.90 (s,1H)	
6a	50/A 188-189 (CH_3CN)		[b]3.82 (s, 6H), 7.00 (d, J=7Hz, 2H), 7.88 (d, J=7Hz, 2H)	[b]55.5, 113.6, 125.9, 130.8, 162.7, 166.9
7a	58/C 163-164 (cyclo-hexane)	306 (M^+, 7); 169 (100); 137 (53); 111 (16)		
8 (x$HClO_4$)	85/B 215-220 (EtOH)	231 (M^+-$HClO_4$, 100); 149(49); 135(41); 42(39)	[b]2.41 (t, J=7Hz, 2H), 3.30 (s, 3H), 3.32 (m, 2H), 3.84, J=7Hz, 2H), 5.05 (sb, 1H), 7.12 (m, 4H)	[b]18.5, 30.8, 32.8, 53.5, 115.6, 122.1, 122.9, 124.8, 127.7, 139.3, 169.2, 170.6

a) all products gave satisfactory microanalysis
b) recorded in DMSO-d_6

Reaction of Bromine with N-Thioacyllactamimines **1**—*Synthesis of Condensed 5-Amino-1,2,4-thiadiazolium bromides* **5**, *3,5-Diaryl-1,2,4-dithiazolium salt* **6a**, *3,5-Diaryl-1,2,4-thiadiazole* **7a** *and 2-(Benzothiazol-2-yl)imino-pyrrolidine* **8** *Hydroperchlorate* (analytical data see Table I)

General Procedure

To a stirred solution of 10 mmol N-thioacyllactamimine **1** in 40 ml acetic acid 10 mmol of bromine were added dropwise. The resulting mixture was shortly heated to reflux and allowed to cool to room temperature.

Method A (**1**: $R^1 = NH_2$, $R^2 = H$, n = 1–4 and R^1 = 4-MeO-Ph, $R^2 = H$, n = 3): The solid was filtered by suction and recrystallized.

Method B (**1**: R^1 = NH-Ph, R^2 = Me, n = 1): After cooling 30 ml of diethyl ether were added. Decanting of the liquid was followed by dissolving the remainder in a small amount of dimethylformamide. 15 mmol of 70% perchloric acid were added cautiously. Precipitation with water yielded the solid perchlorate which was filtered by suction and recrystallized.

Method C (**1**: R^1 = 4-Cl-Ph, R^2 = Me, n = 1): The precipitate was filtered by suction and washed thoroughly with diethyl ether. The solvent was dried and removed in vacuum. The remainder was recrystallized from cyclohexane.

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