J. prakt. Chem. 339 (1997) 152–158

Journal für praktische Chemie
Chemiker-Zeitung

N-Unsubstituted Sulfenamides by Electrophilic Amination of Mercapto Compounds

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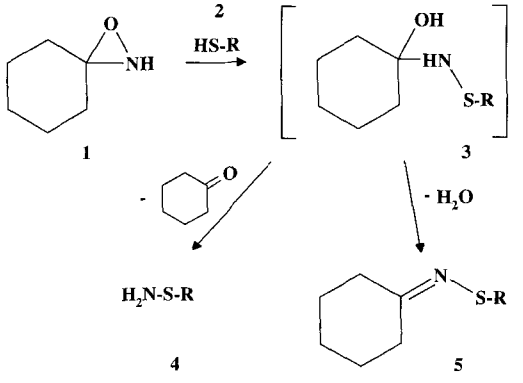
Received June 5th, 1996 respectively September 30th, 1996

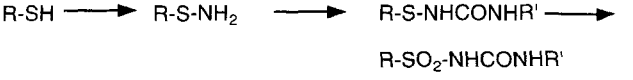
Abstract. Potential mercapto compounds derived from electron deficient heterocycles as 2- and 4-thiouracils, pyridines and pyridine-1-oxide are aminated by the oxaziridine **1** to new sulfenamides (**6**, **9**, **11** and **15** or the isothiazolo-pyridine **14**) which add to phenylisocyanates forming sulfenylureas (**7**, **10**, **12** and **16**). Several other mercapto compounds gave disulfides. Attempts of oxidation of the sulfenamides and the sulfenylureas were unsuccessful. The methylmercapto compound **19** after amination was hydrolyzed to the sulfoxide **20**.

1-Oxa-2-azaspiro[2.5]octane ("3,3-pentamethyleneoxaziridine") **1** is a widely useful NH_2^+-equivalent [1]. The systematic investigation of the synthetic potential of **1** revealed a variety of stabilizing reactions of the primary adduct **3** of (potential) mercapto compounds **2** to the oxaziridine **1**.



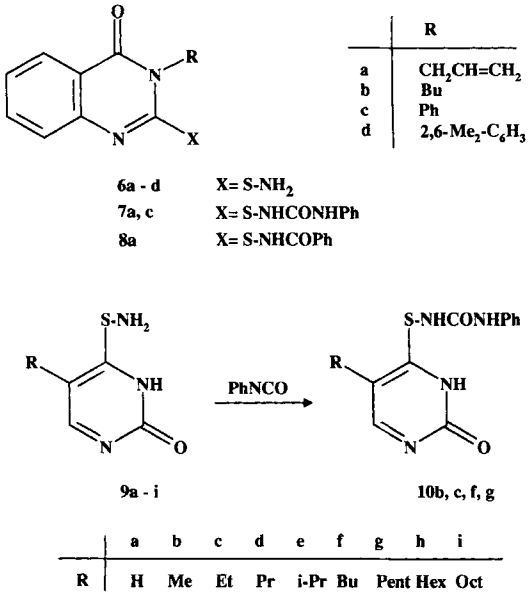
Scheme 1

Conventional preparations of sulfenamides by substitution [2] or *via* sulfenylchlorides [3] give only unsatisfying yields. The formation of the S–N-bond by electrophilic amination with **1** followed by addition of the resulting sulfenamide to an isocyanate and oxydation of the sulfur function could open an alternative route to sulfonylurea derivatives:



Scheme 2

If there are no other stabilizing reactions of the primary adduct **3** (as in polyfunctional nucleophiles, e.g. acylthioureas [4] or 3-unsubstituted 2-thiouraciles [5]), the sulfenamides **4** can be obtained as stable final products. Whereas simple 2-thiouraciles give 5a-amino-5a,6,7,8,9,9a-hexahydro-4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones *via* rearrangement of the corresponding intermediate **3** [5], N^3-substituted 2-mercaptoquinazoline-4-ones ("blocked" 2-thiouracils) yield the sulfenamides **6**. 4-Thiouraciles are converted exclusively and in excellent yields into the sulfenamides **9**. The sulfenamides **6** and **9** add to isocyanates forming the new sulfenylureas **7** and **10**. The benzoylation of **6a** to **8a** was demonstrated.

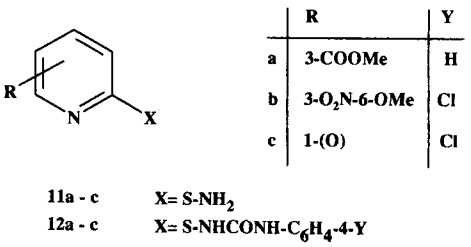


Scheme 3

The sulfenamides **6** and **9** were characterized by their ^{13}C NMR spectra showing a significant upfield shift of about 10 ppm for the carbon atom C2 in comparison with the starting mercapto compounds. The mass spectra have intense molecular ion peaks and the corresponding M–16-signal. All these aminations did not yield the corresponding disulfides of the starting mercapto compound.

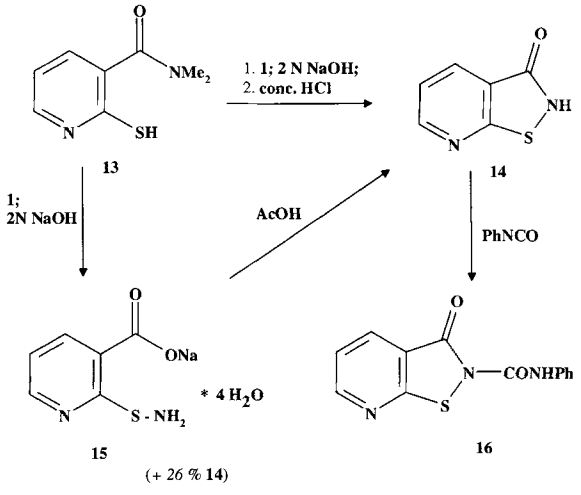
However, several mercapto pyridines and benzenes under similar reaction conditions exclusively gave the known disulfides when treated with the oxaziridine **1**. Some examples of these unwanted conversions are mentioned in table 1.

4-Nitrothiophenol was converted by the oxaziridine **1** to 4-(cyclohexylideneaminothio)-nitrobenzene (66%) with only small amounts of bis(4-nitrophenyl) disulfide (10%) [1]. Therefore, we treated other acceptor substituted 2-mercaptopyridines with **1** and obtained the sulfenamides **11**. They add to isocyanates forming the sulfenylureas **12**.



Scheme 4

Reacting with the oxaziridine **1** in toluene, 2-mercaptonicotinic acid dimethylamide **13** gave only unidentified oily products. However, in the two-phase system toluene/2N NaOH the crystalline amination/hydrolysis product **15** was obtained. On acidification it cyclizes to the isothiazolopyridine-3-ones **14**, which can be obtained also without isolation of the intermediate **15** by working up with hydrochloric acid. The addition to isocyanates proceeds without problems.



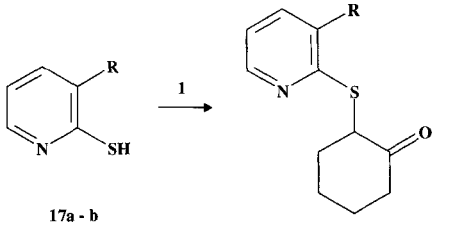
Scheme 5

Table 1 Amination experiments with disulfide formation

starting material	solvent [a]	product [b]	yield
2-mercaptonicotinic acid ethylester	toluene	bis(3-ethoxycarbonylpyrid-2-yl) disulfide	83%
2-mercaptonicotinic acid morpholide	2N NaOH/DMF	bis(3-carboxyl-pyridine-2-yl) disulfide dimethylformamide 1:1 solvate	37%
2-mercaptonicotinic acid	2N NaOH/DMF	bis(3-carboxyl-pyridine-2-yl) disulfide dimethylformamide 1:1 solvate	52%
2- mercaptonicotinic acid	toluene	bis(3-carboxyl-pyridine-2-yl) disulfide diammonium salt	99%
2-mercaptopyridine	toluene	bis(pyridine-2-yl) disulfide	20%
2-mercapto benzoic acid	toluene	bis(2-carboxyphenyl) disulfide	99%
4-acetamino-thiophenol	toluene	bis(4-acetaminophenyl) disulfide	96%

[a]) Experimental conditions as described in the exp. part for the amination procedures, e.g. general procedure 1.
[b]) The disulfides were identical with authentic samples (tlc, *m.p.*).

Other 2-mercaptopyridines, as 2-mercaptonicotinic acid benzylamide **17a** and 3-hydroxy-2-mercaptopyridine **17b** obviously are aminated at the mercapto group. *Via* a cyclohexylidenthioxime rearrangement (details of the mechanism see [5]) and hydrolysis the cyclohexylthiopyridines **18a** and **18b** are formed. In DMSO-d_6 they show different ^{13}C NMR spectra of the cyclohexyl part indicating different tautomeric forms.



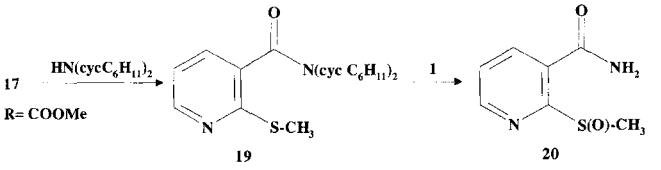
17a - b

18a R= $CONHCH_2Ph$

or enolic form 18b R= OH

Scheme 6

In a curious reaction sequence 2-mercaptonicotinic acid methylester **17** (R= COOMe) and dicyclohexylamine give 2-methylmercaptonicotinic acid dicyclohexylamide **19**. By the action of the oxaziridine **1** the compound **19** is converted to 2-methylsulfoxynicotinic acid amide **20** (cleaveage of the amide group by ammonia from the decomposition of **1** and oxidation of the thioether group). The structures **19** and **20** are in accordance with spectral and microanalytical data. Thus, the NMR signals of the methyl group ($^1H/^{13}C$ ppm in DMSO-d_6) are typical for methyl thioethers (**19**: 2.33/13.6) and sulfoxides (**20**: 3.15/37.5), resp. Probably, in analogy to the formation of **14** the sulfur is aminated and the sulfenamide group displaces the dicyclohexylamine, followed by a hydrolytic ring cleavage of the resulting (unstable) methylsulfenium intermediate. Thus, the oxygen is not transferred directly by the oxaziridine **1**.



Scheme 7

Unfortunately, all attempts of a selective oxidation of the sulfenamides and sulfenylureas described above gave no results of preparative value. Either unchanged starting material, the corresponding disulfides or desulfurization products (2-pyridones) were the only identified compounds.

Financial support by the Hoechst Schering AgrEvo GmbH (Frankfurt, Germany) is gratefully acknowledged. The author thanks Dr. H. Mildenberger and Dr. H. Stark, Hoechst Schering AgrEvo GmbH, for helpful discussions and Mrs. U. Pieper, Institut für Angewandte Chemie e.V. (Berlin), for her skilful assistance in the experiments.

Experimental

Analytical instruments used see ref. [5]. All new compounds gave elemental analyses in accordance with the calculated values.

2-Aminothioquinazoline-4-ones 6 and 4-Aminothiouraciles 9; general procedure 1 (details and analytical data see tables 2–5):

2.0 mmol of the 2-mercaptoquinazoline-4-one (**6**, SH instead of SNH_2) or the 4-mercaptouracile (**9**, SH instead of SNH_2), dissolved in a minimum amount of DMF, are added without cooling to a stirred solution of the oxaziridine **1** in toluene [1]. After few seconds the yellow colour of the starting material disappears, and the title compounds begin to crystallize from the reaction mixture (**9**) or the reaction mixture is evaporated *in vacuo* and the remainder is crystallized by scratching or addition of heptane or ether (**6**).

For a quantitative determination, 0.5 mmol of the sulfenamide is dissolved in glacial acetic acid and treated with an excess of aqueous potassium iodide solution. The iodine liberated is titrated with thiosulfate solution. 100% purity requires 5.00 ml of 0.2N thiosulfate solution. Recrystallized samples of the sulfenamides **6** and **9** show a purity of 96–101%. After titration the starting mercapto compound can be recovered by filtration. The iodometric titration does not give reproducable results with allylic derivatives as **6a**.

Preparation of sulfenyl ureas (7, 10, 12 and 16); general procedure 2 (details and analytical data see tables 2–5)

5 mmol of the sulfenamide, 5 ml dried dioxane (**7**, **10**) or toluene (**12**) and 5.1 mmol of the corresponding isocyanate are refluxed for 15 min (**12**) or one hour (**7**, **10**). The solvent is evaporated in vacuo. The remainder is collected or brought to crystallization by scratching with ether and recrystallized.

3-Allyl-2-benzoylaminothio-4-oxoquinazoline **8a** *(analytical data see tables 2–3)*

0.3 g (2.1 mmol) benzoylchloride are added to a stirred and ice cooled solution of 0.47 g (2 mmol) **6a** in 5 ml dry pyridine. After one hour at 0 °C and two hours at 20 °C the reaction mixture is shaken with cold water and chloroform. The chloroform layer is washed with water, dried and evaporated. The remaining oil crystallizes on scratching with ethanol; 0.35g **8a** (52%), *m.p.* 168 °C (EtOH); $C_{18}H_{15}N_3OS$ (337.39).

2-Aminothio-3-methoxycarbonylpyridine **11a**

7.3 g (43 mmol) 2-mercaptonicotinic acid methylester **17** (R= COOMe) in a small amount of DMF and a solution of 64 mmol **1** in toluene are stirred. The temperature raises to 30 °C

Table 2 4-Oxoquinazolines **6**, **7** and **8** (general procedures 1 and 2) and their mass spectra

Compd.	formula	mol. wt.	yield (%)	*m.p.* (°C)/solvent	MS [*m/e* (relative intensity)]
6a	$C_{11}H_{11}N_3OS$	233.30	68	92/heptane 122/AcOEt [a]	233 (26); 162 (100), 203 (63), 204 (52), 145 (32), 90 (32)
6b	$C_{12}H_{15}N_3OS$	249.33	97	62–64/hexane	249 (40); 233 (100), 145 (55), 162 (41), 179 (35), 90 (27)
6c	$C_{14}H_{11}N_3OS$	269.32	71	168/EtOH	269 (100); 77 (97), 236 (86), 221 (83), 90 (48), 48 (35)
6d	$C_{16}H_{15}N_3OS$	297.39	70	214–215/EtOH	297 (29); 120 (100), 77 (30), 90 (24), 48 (20), 119 (17)
7a	$C_{18}H_{15}N_3OS$	352.41	78	183–184/*i*PrOH	352 (5); 93 (100), 192 (92), 203 (87), 217 (51), 119 (55)
7c	$C_{21}H_{16}N_3OS$	388.44	60	223–235/MeCN	388 (2); 296 (100), 253 (94), 312 (51), 221 (50), 77 (44)
8a	$C_{18}H_{15}N_3OS$	337.39	52	168/*i*PrOH	337 (0.3); 105 (100), 51 (87), 52 (73), 77 (69), 201(61)

[a]) polymorphism.

Table 3 ^{13}C (first line) and ^1H (second line) NMR spectra of the compounds **6**, **7** and **8**

Compd.	C2	C4	C4a	C5	C6	C7	C8	C8a	R
6a	163.1	160.2	118.5	126.5	134.6	125.5	125.8	147.1	44.2/131.3/117.5 [a])
	–	–	–	8.10m	7.82m	7.45m	7.60m	–	4.55m/5.90m/5.15m; SNH_2 4.32s
6b	162.9	160.4	118.6	126.4	134.5	125.5	125.7	147.0	42.2/29.7/19.5/13.4 [b])
	–	–	–	8.06m	7.81m	7.44m	7.64m	–	3.87t/1.1–1.9m, 4H/ 0.93t [b]); SNH_2 4.06s
6c	163.5	160.5	119.3	126.6	134.2	125.6	125.9	147.4	134.8/129.4/129.1/ 130.0 [c]);
	–	–	–	8.11m	7.85m	7.49m	7.65m	–	7.4–7.9m, 2H/7.57m, 3H; SNH_2 4.12s
6d	163.6	159.6	118.9	126.8	135.2	125.8	126.0	147.7	136.2/136.2/128.7/ 130.1[c]); CH_3 17.0
	–	–	–	8.14m	7.88m	7.38m	7.69m	–	7.28d, 2H/7.50t, 1H; CH_3 2.04s; SNH_2 4.20s
7a	157.9	160.2	117.9	126.5	134.8	126.0	126.0	146.8	44.6/131.1/118.1[a]); 154.5/139.2/118.8/ 128.7/122.5 [d])
7c	158.2	160.5	118.8	126.6	134.9	126.1	126.1	147.2	R:133.8/129.3/129.6/ 130.4 [c]); 154.4/139.2/118.7/ 128.7/122.4 [d])
8a	156.5	160.7	118.7	126.5	134.8	126.1	126.1	146.7	44.8/131.1/117.9 [a]); 168.8/133.5/128.1/ 128.5/132.2 [d])
	–	–	–	7.4m			8.2m	–	4.69d/5.8–6.2m/5.1–5.4m [a]);7.2–7.9m, 5H; NH 10.2s

[a]) $NCH_2/CH=/=CH_2$; [b]) $NCH_2/CH_2/CH_2/CH_3$; [c]) C1/C2,6/C3,5/C4; [d]) CO/C1/C2,6/C3,5/C4.

and the yellow color of the starting material disappears. After one hour some precipitated bis-(3-methoxycarbonylpyrid-2-yl)-disulfide (1.08 g, 15%; *m.p.* 191–193 °C after recrystallisation from ethanol) is removed by suction. The filtrate is evaporated *in vacuo*. The residue is treated with ether and yields **11a**; 4.12 g (52%); *m.p.* 137–138 °C (from methanol); $C_7H_8N_2O_2S$ (184.22). – ^1H NMR: δ OMe 3.81s (3H), H4 8.11d (1H), H5 7.16t (1H), H6 8.65d (1H). – ^{13}C NMR: δ C2 168.8, C3 120.0, C4 138.4, C5 118.8, C6 152.5, CO 165.0, OMe 52.3. – MS (70 eV): 184 (M^+, 70 %), 78 (53 %), 153 (36 %), 48 (28 %), 50 (25 %), 47 (23 %).

2-Aminothio-6-methoxy-3-nitropyridine **11b**

1.56 g (8.4 mmol) 2-mercapto-6-methoxy-3-nitropyridine (*m.p.* 74–75 °C) and a solution of 13 mmol **1** in toluene are stirred. After few seconds the starting material dissolves and **11b** precipitates; 1.0 g, 59%; *m.p.* 192 °C (EtOH); $C_6H_7N_3O_3S$ (202.21). – ^1H NMR: δ OMe 3.34s (3H), H4 8.11 AB (*J*= 8.8

Table 4 4-Aminothiouraciles **9** and 4-phenylaminocarbonylaminothiouraciles **10** (general procedures 1 and 2) and their mass spectra

Compd.	formula	mol. wt.	yield (%)	*m.p.* (°C)/solvent	mass spectra (*m/e* [relative intensity])
9a	$C_4H_5N_3OS$	143.17	98	160/EtOH	143 (7); 58 (100), 45 (66), 128 (60), 57 (56), 52 (42)
9b	$C_5H_7N_3OS$	157.20	87	196–197/EtOH	157 (100); 140 (76), 141 (60), 54 (57), 81 (56), 82 (35)
9c	$C_6H_9N_3OS$	171.23	95	191/EtOH	171(45); 153 (100), 155 (48), 154 (34), 86 (15), 127 (13)
9d	$C_7H_{11}N_3OS$	185.26	93	181/EtOH	185 (45); 153 (100), 169 (70), 185 (45), 167 (31), 113 (29)
9e	$C_7H_{11}N_3OS$	185.26	82	193–194/EtOH	185 (43); 153 (100), 167 (82), 169 (43), 168 (23), 170 (20)
9f	$C_8H_{13}N_3OS$	199.28	71	172/EtOH	53 (100); 183 (43), 113 (31), 199 (24), 81 (24), 86 (19)
9g	$C_9H_{15}N_3OS$	213.31	93	167–168/EtOH	213 (47); 153 (100), 197 (52), 113 (29), 141 (23), 165 (21)
9h	$C_{10}H_{17}N_3OS$	227.34	86	172/EtOH	227 (28); 153 (100), 211 (45), 113 (36), 179 (35), 141 (26)
9i	$C_{12}H_{21}N_3OS$	255.39	81	182/EtOH	55 (18); 153 (100), 207 (99), 239 (50), 81 (46), 141 (41)
10b	$C_{12}H_{12}N_4O_2S$	276.33	56	198/DMSO/H_2O	276 (0.2); 93 (100), 119 (43), 142 (32), 91 (30), 222 (7)
10c	$C_{13}H_{14}N_4O_2S$	290.35	66	190–192/DMF/EtOH/H_2O	290 (0.4); 93 (100), 119 (77), 64 (56), 155 (48), 91 (47)

Table 5 ^{13}C- (first line) and ^{1}H- (second line) NMR spectra of the compounds **9** and **10**

Comp.	C2	C4 (SNH_2)	C5	C6 (H6)	R
9a	149.8	190.3	111.3	140.5	–
	–	4.27s	6.57 [a]	7.74 [a]	
9b	155.0	182.8	116.1	139.9	12.3
	–	3.7br.s	–	7.36s	1.85s
9c	155 [b]	182 [b]	117.5	146.6	18.4/11.8
	-	3.44	–	7.37s	2.20q, 1.04t
9d	154.2	182.6	111.5	140.2	28.0/21.4/13.3
	–	3.8br.s	–	7.41s	2.18t/1.45sext/0.84t
9e	154.0	182.0	118.2	138.1	25.2/22.1
	–	3.8br.s	–	7.43s	2.59sept/1.09d
9f	154.2	182.6	111.7	140.1	30.5/25.7/21.6/13.5
	–	3.80s	–	7.39s	2.23t/1.1–1.6m, 4H, 0.90t
9g	154 [b]	182 [b]	112 [b]	140.2	30.7/26.0/25.7/20.8/13.8
	–	3.8br.s	–	7.33s	2.20t/1.3br.m, 6H/0.86t
9h	154.2	182.6	111.7	140.2	30.8/28.3/28.1/26.0/21.9/13.8
	–	3.8br.s	–	7.32s	2.19t/1.3br.m, 8H/0.85t
10b	154.1*	178.1	107.0	141.7	11.5; 154.4*/139.3/118.4/128.7/122.3 [c]
	–	7.9/9.1	–	7.43s	1.94s; 7.1–7.6m
10c	154.1*	177.8	113.2	140.8	19.2/13.0; 154.4*/139.3/118.4/128.6/122.2 [c]
	–	7.9/9.1	–	7.39s	2.28q/1.09t; 6.9–7.5br.m
10f	153.9*	177.8	111.8	141.4	30.6/25.7/21.6/13.5; 154.3*/139.3/118.3/128.7/122.2 [c]
	–	7.8/9.0	–	7.44s	2.30t/1.4br.m, /0.90t
10g	153.9*	177.7	111.8	141.4	30.7/28.1/25.9/21.7/13.8; 154.3*/139.2/118.3/128.7/122.2 [c]
	–	7.8/9.1	–	7.43s	2.28t/1.2–1.6m, 6H/0.86t;

* assignments not clear; [a] AB-system, J_{AB}= 7 Hz; [b] very low solubility/intensity; [c] CO/NHPh C1/C2,6/C3,5/C4.

Hz, 2H) H5 6.73, NH_2 4.1br.s (2H). – ^{13}C NMR: δ C2 167.6, C3 133.9, C4 136.9, C5 106.8, C6 165.1, OMe 55.0. – MS (70 eV, *m/e*): 201 (M, 56%), 108 (100%), 137 (90%), 80 (83%), 64 (65%), 96 (45%), 48 (50%), 136 (36%).

2-Aminothiopyridine-1-oxide **11c**

0.77 g (6.1 mmol) 2-mercapto-pyridine-1-oxide (precipitated freshly from an aqueous solution of the sodium salt by 2N sulfuric acid) and a solution of 19 mmol **1** in toluene are stirred over night. Precipitated **11c** is separated by suction and washed with ether; 0.78 g, 90%; *m.p.* 163 °C (DMF/toluene); $C_5H_6N_2OS$ (142.19). – ^{1}H NMR: δ H3 7.52dd, H4 7.42dt, H5 7.14dt, H6 8.19dd; NH_2 4.00s (2H). – ^{13}C NMR: δ C2 157.9, C3 125.4, C4 120.5, C5 120.1, C6 137.8. – MS (70 eV, *m/e*): 142 (M^+, 50%), 78 (100%), 125 (50%), 79 (53%), 51 (30%), 98 (24%), 69 (18%).

3-Methoxycarbonyl-2-phenylaminocarbonylaminothiopyridine **12a**

As described in the general procedure 2, 4.3 g (23.4 mmol) **11a** and 2.54 ml (23.4 mmol) phenylisocyanate give **12a**; 6.2 g (87%); *m.p.* 210–212 °C (DMF/toluene); $C_{14}H_{13}N_3O_3S$ (303.33). – ^{1}H NMR: δ OMe 3.86s (3H), H4 8.20d (1H), H5 7.2 (superposed by Ph), H6 8.61d (1H); Ph 6.8–7.6 m (6H including H5). – ^{13}C NMR: δ NHPh C1 139.6, C2/6 128.6, C3/5 118.3, C4 121.9; CONH 155.3; MeO 52.5, COOMe 164.2; C2 165.2, C3 120.4, C4 138.6, C5 119.9, C6 152.8. – MS (70 eV, *m/e*): 303 (M^+, 9%), 152 (45%), 211 (43%), 93 (39%).

2-(4-Chlorphenylaminocarbonylaminothio)-6-methoxy-2-nitropyridine **12b**

As described in the general procedure 2, 0.2 g (1 mmol) **11b** and 0.15 g (1 mmol) 4-chlor-phenylisocyanate give **12b**; 0.3 g (85%); *m.p.* 245–255 °C (DMF/toluene); $C_{13}H_{11}N_4ClO_4S$ (354.78). – ^{1}H NMR: δ OMe 3.36s (3H), H4 8.13 AB (J= 8.8 Hz, 2H) H5 6.77, 4-Cl–C_6H_4 7.30/7.47 (AB system, 4H). – ^{13}C NMR: δ C2/C6 165.3/162.1, C3 134.4, C4 137.2 C5 108.2; MeO 54.7; CO 155.6; 4-Cl-C_6H_4 C1 138.6, C2/C6 120.4, C3/C5 128.8, C4 126.2. – MS (70 eV, *m/e*): 354/356 (M^+, 22%/8 %), 137 (100%), 99 (80%), 127 (74%), 126 (54%), 64 (52%), 111 (47%), 185 (39%), 96 (39%), 108 (36%).

2-(4-Chlorphenylaminocarbonylaminothio)pyridine-1-oxide **12c**

0.28 g (2 mmol) **11c** and 0.3 g (2 mmol) 4-chlor-phenylisocyanate give **12c**; 0.55 g (93%); *m.p.* 213 °C (DMF/toluene); $C_{12}H_{10}N_3ClO_2S$ (295.75). – ^{1}H NMR: δ H3 7.48m (1H), H4/H5 7.18–7.35m (2H), H6 8.31dd (1H); 4-Cl-C_6H_4 7.32/7.50 (AB system, 4H), NH 9.31s/8.04s. – ^{13}C NMR: δ C2 153.5, C3 126.5, C4 121.7, C5 119.8, C6 138.0; CO 154.9; 4-Cl-C_6H_4 C1 138.5, C2/C6 120.5, C3/C5 128.7, C4 126.2. – MS (70 eV, *m/e*): 295 (M^+, 0.5%), 127 (100%), 90 (60%), 78 (45%), 153 (40%), 125 (25%), 154 (15%).

3-Oxo-1,2-thiazalo[4,5-b]pyridine (**14**)

1.82 g (10 mmol) 2-dimethyl-aminocarbonyl-2-mercaptopyridine **13**, 15 mmol **1** in toluene, 25 g ice and 5 ml 2N NaOH are shaken in separatory funnel for 20 min. The aqueous phase is acidified with concentrated hydrochloric acid, the precipitated product is washed with water.; 1.00 g (66%) **14**, *m.p.* 246–246.5 °C (DMF/EtOH 1:1); $C_6H_4N_2OS$ (152.18). – ^{1}H NMR: δ Py H4 8.32m, H5 7.51m, H6 8.82m; NH 11.9br.s. – ^{13}C NMR: δ Py C2 162.9, C3 118.4, C4 133.0, C5 120.2, C6 152.4; CO 167.7. – MS (70 eV, *m/e*): 152 (M^+, 100%), 97 (40%), 78 (37%), 77 (22%), 70 (22%), 124 (13%).

Sodium salt of 2-aminothionicotinic acid tetrahydrate (**15**)

A crystalline precititate from the alkaline reaction mixture of the preparation of **14** is isolated and recrystallized from EtOH; 0.9 g (34%) **15**, *m.p.* > 360 °C. The acidified aqueous phase yields 0.4 g (26%) **14**. Warming of crude **15** with acetic acid for 1 min. gives **14** (68% yield); $C_6H_{13}N_2NaO_6S$ (263.24). – ^{1}H NMR: δPy H4 8.08m, H5 7.19m, H6 8.51m. – ^{13}C NMR: δ Py C2 171.0*, C3 123.2, C4 132.5, C5 117.7, C6 149.1; CO 171.6*. – MS (70 eV, *m/e*): 152 (100%), 64 (75%), 48 (75%), 46 (60%), 51 (50%), 47 (50%), 76 (35%), 78 (30%), 70 (30%).

3-Oxo-2-phenylaminocarbonyl-1,2-thiazolo[4,5-b]pyridine (**16**)

350 mg (2.29 mmol) **14**, 5 ml toluene and 320 mg (2.7 mmol) phenylisocyanate are refluxed for one hour. After cooling the separated crystals are collected; 550 mg (89%) **16**, *m.p.* 165–167 °C (EtOH); $C_{13}H_9N_3O_2S$ (271.31). – ^{1}H NMR: δ Py H4 7.84m, H5 7.61m, H6 8.97m; NH 10.8br.s; Ph H2/H6 7.59m (2H), H3/H5 7.41m (2H), H4 7.19m (1H). – ^{13}C NMR: δ Py C2 161.4, C3 118.4, C4 136.0, C5 124.9, C6 152.7, CO 163.7; CONHPh CO 156.2, Ph C1 136.7, C2/C6 120.3, C3/C5 129.3, C4 122.0. – MS (70 eV, *m/e*): 271 (M^+, 6%), 152 (100%), 119 (40%), 91 (20%), 64 (14%), 98 (10%), 78 (10%).

3-Benzylaminocarbonyl-2-(2-oxocyclohexylthio)pyridine (**18a**)

0.57 g (2.34 mmol) **17a** and 3.5 mmol **1** in toluene (see general procedure 1) give after scratching with petroleum ether 0.65 g (82%) **18a**, *m.p.* 120–122 °C, after recrystallization from EtOH 139–140 °C; $C_{19}H_{20}N_2O_2S$ (340.44). – ^{1}H NMR: δ Py H4 7.84m, H5 7.19m, H6 8.46m; NH 9.08t; CH_2 4.45d (2H) Ph 7.2–7.4m (5H); cyclohex SCH 4.72m, H3–H6 1.2–2.4m (8H). – ^{13}C NMR: δ Py C2 156.1, C3 118.9, C4 135.3, C5 126.7, C6 149.7, CONH 166.0; CH_2Ph CH_2 42.5, Ph C1 139.0, C2/C6 128.2, C3/C5 129.2, C4 129.6; cyclohex C1 52.4, C2 205.9, C3 41.2, C4 26.8, C5 24.5, C6 33.9. – MS (70 eV, *m/e*): 340 (M^+, 18%), 323 (100%), 91 (32%), 324 (23%), 106 (18%), 197(14%), 213 (13%).

3-Hydroxy-2-(2-hydroxycyclohexenylthio)-pyridine (**18b**)

0.63 g (5 mmol) **17b**, 15 g of crushed ice, 2,5 ml (5 mmol) 2N NaOH and 7.5 mmol **1** in toluene (see general procedure 1) are shaken for 10 min. The aqueous layer is separated, acidified with concentrated HCl, evaporated and dried under reduced pressure. The residue is extracted with ethanol, filtered from NaCl and treated with ether giving 0.7 g (63%) **18b**, *m.p.* 190–195 °C (from toluene/DMF); $C_{11}H_{13}NO_2S$ (223.30). – ^{1}H NMR: δ Py H4 7.92m, H5 7.72m, H6 8.49m; OH 12.9; CH_2 2.03m (4 H)/1.59m (4 H). – ^{13}C NMR: δ Py C2 152.3, C3 153.2, C4 104.0, C5 129.0, C6 143.3; cyclohex C1 50.7, C2 153.2, C3 38.8, C4 20.6, C5 19.7, C6 23.5. – MS (70 eV, *m/e*): 223 (M^+, 30%), 206 (60%), 162 (30%), 128 (30%), 127 (100%), 96 (65%), 83 (40%), 55 (30%).

3-Dicyclohexylaminocarbonyl-2-methylthio-pyridine (**19**)

0.85 g (5 mmol) 2-mercaptonicotinic acid methylester **17** (R= COOMe) and 1.08 g (6 mmol) dicyclohexylamine are heated at 150 °C for 10 min. The TLC indicates complete conversion. The product is washed with ether leaving 1.45 g (87%) **19**, *m.p.* 168–170 °C (from *n*-heptane); $C_{19}H_{28}N_2OS$ (332.52). – ^{1}H NMR: δ Py H4 8.05m, H5 7.10m, H6 8.44m; CH_2 1.0–2.1m (20 H), CH 3.08t (2 H); SCH_3 2.33s (3 H). – ^{13}C NMR: δ Py C2 159.5, C3 132.0, C4 137.0, C5 117.9, C6 148.5; CO 167.9; SCH_3 13.6; cyclohex C1 51.8, C2/C6 29.0/24.1, C3/C5 24.1/24.1, C4 24.9. – MS (70 eV, *m/e*): 133 (100%), 106 (14%), 78 (78%), 77 (68 %).

3-Aminocarbonyl-2-methylsulfinyl-pyridine (**20**)

1.45 g (4.36 mmol) **19** in 4 ml DMF and 7 mmol **1** in toluene (see general procedure 1) give after stirring overnight 0.5 g (62%) **20**, *m.p.* 164–165 °C (from EtOH); $C_7H_8N_2O_2S$ (184.22). – ^{1}H NMR: δ Py H4 8.34m, H5 7.76m, H6 8.74m; NH_2 5.61s; CH_3 3.15s. – ^{13}C NMR: δ Py C2 152.4, C3 132.8, C4 140.3, C5 127.8, C6 151.5, CO 166.3; CH_3 37.5. – MS (70 eV, *m/e*): 184 (M^+, 10%), 183 (20%), 169 (100%), 152 (65%), 151 (75%), 138 (85%), 136 (30%), 124 (75%), 123 (50%), 122 (45%), 79 (85%).

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