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FROM HALOQUINOLINES AND HALOPYRIDINES TO QUINOLINE- AND PYRIDINESULFONYL CHLORIDES AND SULFONAMIDES

Andrzej Maślankiewicz,[a)] * Krzysztof Marciniec,[a)] Maciej Pawłowski,[b)] and Paweł Zajdel[b)]

[a)] Department of Organic Chemistry, The Medical University of Silesia Jagiellońska 4, 41-200 Sosnowiec, Poland

[b)] Department of Medicinal Chemistry, Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Kraków,Poland

E-mail: maslankiewicz@slam.katowice.pl

Abstract– The action of sodium methanethiolate (in boiling DMF) towards haloazines (*i.e.* chloro- or bromo-pyridines and quinolines) (**1**) (with halogen substituent in *non-aza*-activated position) causes sequentially halogen *ipso-substitution* to methylthioazines (**2**) and then *S-demethylation* to azinethiolates (**3A**), which were: i) subjected to *S*-methylation, ii) oxidized to diazinyl disulfides (**4**) and iii) oxidatively chlorinated to azinesulfonyl chlorides (**5**). α- and γ-pyridine- and quinolinesulfonyl chlorides (**5a**, **5c**, **5d** and **5f**) were prepared by oxidative chlorination of respective disulfides (**4**) performed in conc. hydrochloric acid and characterized by ^{1}H and ^{13}C NMR spectra. All azinesulfonyl chlorides (**5**) were effectively converted to corresponding azinesulfonamides (**6**).

INTRODUCTION

Compounds containing an azinesulfamoyl moiety are of considerable interest since they exhibit diverse biological activities with numerous therapeutic applications.[1] They have been shown to inhibit several enzymes as well as to modulate the activity of many receptors. Several pyridinesulfonamides showed antitumor activity,[2] while 4-amino-3-pyridinesulfonylurea derivatives, including drug e.g. *torasemide*, were potent diuretic agents.[3] Some quinolinesulfamoyl derivatives exerted anti-HIV-1 activity,[4,5] other displayed neuroprotective, antistroke, anticancer or antiviral properties.[1] They also inhibited carbonic anhydrase and thus acted as very potent antidiabetics, diuretics or topically acting antiglaucoma agents.[6] Furthermore, quinolinesulfonamides showed antiinflammatory and immunomodulating properties[7] as well being classified as potent and selective β_3 receptor agonists with therapeutic potential for the treatment of diabetes type II and obesity.[8,9] Next, the quinolinesulfonamide moiety has been recently found in compounds acting through the CNS receptor[9] and compounds targeting pathomechanisms involved in Alzheimer's disease.[10]

Azinesulfonic acids (sometimes in the form of their sodium salt) with the sulfonic substituent in the *aza*-activated position can be obtained in reactions of haloazines with sodium sulfite,[11,12] or by careful oxidation of respective thioazines.[11-15]

Azinesulfonic acid with the sulfonic substituent in *non-aza*-activated position can be prepared by direct sulfonation,[16,17,18] by oxidation of respective thioazines[11,15] or by work-consuming cyclisation.[17,19,20] To the best of our knowledge, there exists no general preparative method for isomeric azinesulfonic acids.

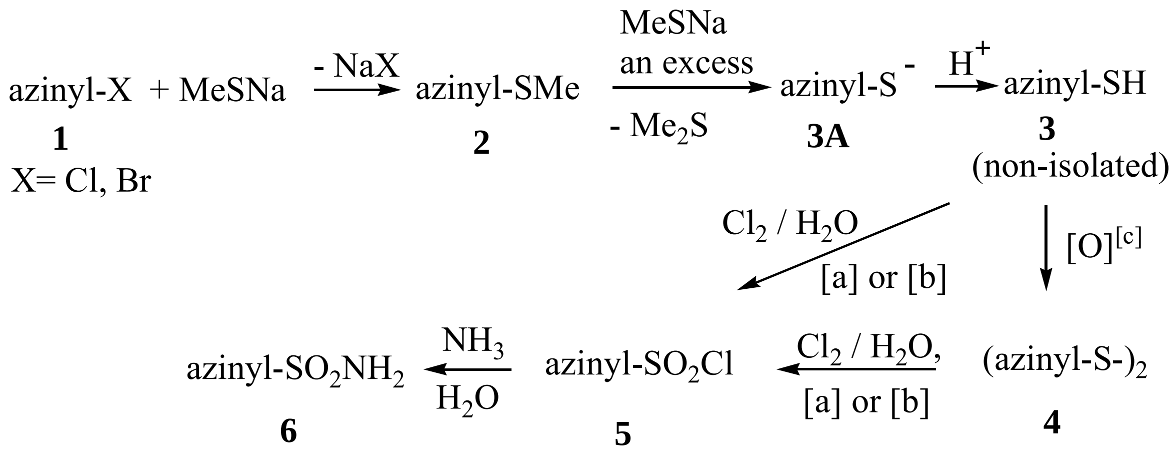
As the azinesulfamoyl moiety is more and more frequently incorporated in molecules of biologically active compounds,[1-10] we considered elaboration of a more universal method of preparation of azinesulfonyl chlorides as a source of building blocks for the generation of azinesulfonic acid derivatives libraries.

RESULTS AND DISCUSSION

We chose haloazines (pyridines and quinolines) (**1**) as common substrates since they are easily available derivatives of azines[21,22] and because *sulfido-de-halogenation* in haloazines was mentioned several times in the literature.[23-27] The key-inspiration for the present study comes from the paper of Testaferri, Tiecco, Tingoli *et al*.,[27] who stated that treatment of haloarenes and some haloheteroarenes with an excess of sodium alkanethiolate could be arranged as a *one-pot* process, leading directly and effectively to sodium arene- or azinethiolates. Whereas the authors mentioned above trapped thiolates by methylation,[27] we decided to trap azinethiolates (**3A**) by oxidation, first to diazinyl disulfides (**4**) and then to azinesulfonyl chlorides (**5**).

In the case of azinesulfonyl chlorides (**5b**, **e**, **g**, **h**, **i**, **j** and **k**) with the sulfonyl group in the *non-aza*-activated position, the experimental protocol was composed of three main stages discussed in details below: i) preparation of methylthioazines (**2**) or azinethiolates (**3A**) from haloazines (**1**) and sodium methanethiolate, ii) oxidation of crude azinethiols (**3**) or azinethiolates (**3A**) to diazinyl disulfides (**4**) or to azinesulfonyl chlorides (**5**), iii) amination of **5** to azinesulfonamides (**6**). In the first stage, sodium methanethiolate (*ca.*1.5 mol. eqv.) in boiling DMF (within 1 h) appeared to be sufficiently reactive for the purpose of *methylthio-de-halogenation* of bromo- and chloroazines (**1**) to methylthioazines (**2**) (yield up to 60 %) accompanied by azinethiolates (**3A**) (*ca*. 21-25 %) (Table, entries 7.1, 8.1). Furthermore, methylthioazines (**2**) treated within the same reaction system underwent complete *methylthio-S-demethylation* to azinethiolates (**3A**). To remove the excess of methanethiol derivatives, the mixture was evaporated to dryness, diluted with cold water, acidified with conc. hydrochloric acid and the volatile compounds were evaporated under vacuum. The resulting mixture of azinethiol (**3**) and inorganic salts was either oxidized to diazinyl disulfides (**4**) with potassium ferricyanide[28] or subjected to oxidative-chlorination ('wet'-chlorination)[29] to azinesulfonyl chlorides (**5**). Both sub-stages with the use of sodium methanethiolate could be combined and arranged after oxidation as a process leading directly from haloazine (**1**) to disulfides (**4**) or to azinesulfonyl chlorides (**5**). Due to the low basicity of azinesulfonyl chlorides (**5**), they were precipitated from acetic acid or conc. hydrochloric acid solutions by dilution with water.

Scheme



[a] 80 % AcOH, 10 °C, [b] conc. HCl aq, 0 °C, [c] aq. $K_3Fe(CN)_6$ / OH^-

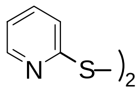
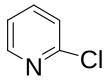
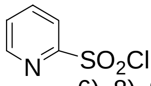
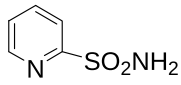
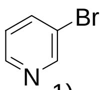
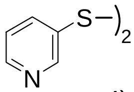
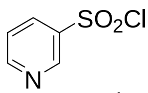
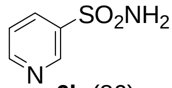
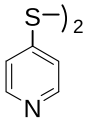
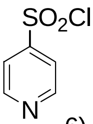
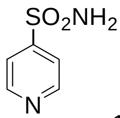
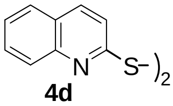
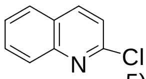
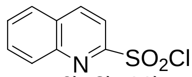
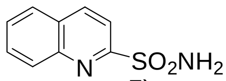
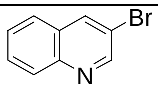
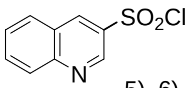
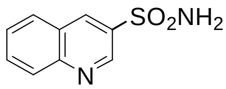
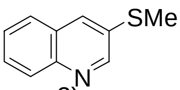
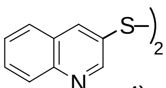
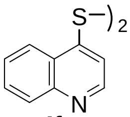
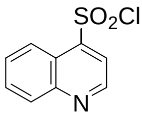
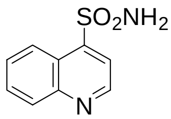
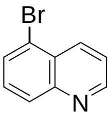
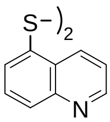
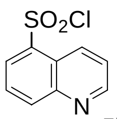
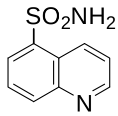
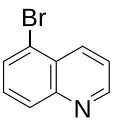
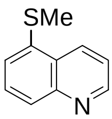
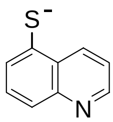
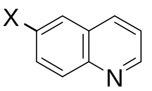
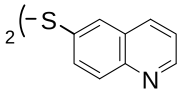
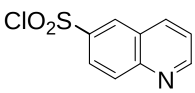
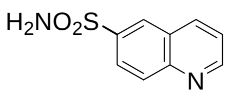
Azinesulfonyl chlorides (**5b**, **e**, **g**, **h**, **i**, **j**) were stable when stored at room temperature except 4-isoquinolinesulfonyl chloride (**5k**), which underwent partial decomposition with evolution of sulfur dioxide even at 5 ºC. All azinesulfonyl chlorides (**5**) were successfully converted to the respective azinesulfonamides (**6**).

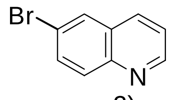
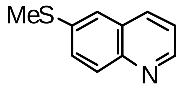
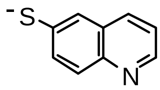
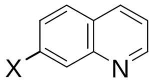
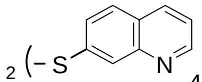
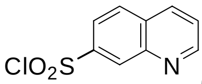
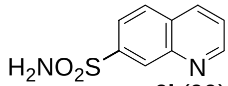
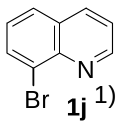
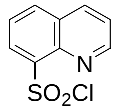
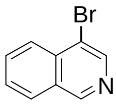
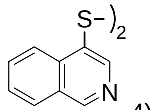
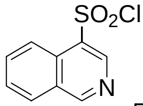
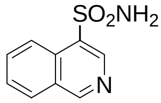
Introduction of thio-substituent by replacement of halogen in azine *aza*-activated positions is much easier than in other isomers. High reactivity of halogen substituent at α- and γ-positions of azines toward the action of *S*-nucleophiles was observed in reactions with sodium sulfide,[23a,b, 24] potasssium hydrogen sulfide,[25,26] sodium alkane and arenethiolates,[27,30] sodium thiosulfate,[31] thiourea,[32,33] and even in reactions with sodium sulfite.[11,12]

Divalent sulfur derivatives of azines (thiones *vs* thiols, disulfides) could be oxidized to the respective azinesulfonic acids by careful oxidation of respective thioazines.[11-15] However, none of azinesulfonic acids or of their sodium salts (with sulfonic substituent in the *aza*-activated position) could be converted to azinesulfonyl chloride after treatment with phosphorus chlorides (PCl_5 or $POCl_3$)[34,13] or with thionyl chloride [11] as well as with benzylidyne chloride.[34] Nevertheless, oxidative-chlorination performed in

80 % aqueous acetic acid (gaseous chlorine, 0-20 ºC) also causes final splitting of C(α- or γ-azinyl)-S-bond and leads to chloroazine and sulfate anion.[29]

Table

Entry	Substrate or substrate system	Product, yield [%], procedure	Sulphonamide **6**, 7) (yield) [%]
1.	 **4a**	 **1a** (82) 5) |  **5a** 6), 8), 9)	 **6a** (62) 9)
2.	 + MeSNa **1b** 1)	 **4b** (82) 4) |  **5b** (81) 5)	 **6b** (86)
3.	 **4c**	 **5c** 6), 8)	 **6c** (32) 10)
4.	 **4d**	 **1c** (92) 5) |  **5d** 6), 8), 11)	 **6d** (78) 7)
5.	 +MeSNa **1d** 1)	 **5e** (88) 5), 6)	 **6e** (91)
5.1.	 + MeSNa **2d** 3)	 **4e** (82) 4) |  **5e** (88) 6)	
6.	 **4f**	 **5f** 6), 8)	 **6f** (67)
7.	 + MeSNa **1e** 1)	 **4g** (75) 4) |  **5g** (86) 5)	 **6g** (92) 7)
7.1.	 + MeSNa **1e** 2)	 **2a** (56) 2) +  (24) 13)	-
8.	 + MeSNa(K) **1f** (X=Cl), **1g** (X=Br) 1), 12)	 **4h** (88) 4) |  **5h** (89) 5), 6)	 **6h** (87)

8.1	 + MeSNa **1g** 2)	 +  **2b** (58) 2) (26) 13)	-
9.	 + MeSNa(K) **1h** (X=Cl), **1i** (X=Br) 1), 12)	 |  **4i** (85) 4) **5i** (84) 5), 6)	 **6i** (90)
10.	 + MeSNa **1j** 1)	 **5j** (89) 5)	 **6j** (91)
11.	 + MeSNa **1k** 1)	 |  **4k** (86) 4) **5k** (81) 5)	 **6k** (87)

1) Procedure A; 2) Procedure B; 3) Procedure C; 4) Procedure D; 5) Procedure E; 6) Procedure F; 7) Procedure G. 8) Non-isolated in the pure form, characterized by ^{1}H and ^{13}C NMR spectra as well as by amination. 9) Could be also prepared from 2(1*H*)-pyridinethione, ref.,[5, 26, 34, 40]. 10) Prepared also from 4(1*H*)-pyridinethione, ref.,[34]. 11) Prepared also from 2(1*H*)-quinolinethione, ref.,[35]. 12) Potassium thiomethanolate was used for the reaction with chloroquinolines (**1f**) and (**1h**). 13) Characterized by methylation in the form of methylthioquinoline (**2**).

The same treatment of 2(1*H*)-quinolinethione or 2,2'-diquinolinyl disulfide (**4d**), performed in the course of this work, also led to 2-chloroquinoline in 92 % yield. Fortunately, Talik and Płażek[34] discovered that careful treatment of conc. hydrochloric acid solution of 2(1*H*)-pyridinethione and even 4(1*H*)-pyridine thione with gaseous chlorine at -10 ºC – 0 ºC may be a preparative source of 2- and 4-pyridinesulfonyl chlorides (**5a** and **5c**). Although both isomers are very unstable compounds, the 2-isomer **5a** could be isolated in pure form (at – 70 ºC) and characterized by elemental analysis. However, due to the instability of the 4-isomer **5c**, its solutions should be immediately consumed in further processes, e.g. amination.[34] Talik and Płażek's procedure[34] was confirmed later for 2-pyridinesulfonyl chloride (**5a**)[5,40] and was applied to the preparation of 3- and 4-quinolinesulfonyl chlorides (**5e** and **5f**),[26] however both isomers were not obtained in the pure form, moreover, the mp's of compound **5f** (109-111 ºC)[26] is according to our experience not possible to reach. The preparation of 2-quinolinesulfonyl chloride (**5d**) by chlorination of 2(1*H*)-quinolinethione in water and in the presence of ferric chloride was also mentioned in a French patent.[35]

The chlorination of hydrochloric acid solution of all thioazines (**3** and **4**) was successfully applied to the preparation of all quinoline- and pyridinesulfonyl chlorides (**5**) described in this paper. (see Table) Stability of (**5d** and **5f**) was the same as that of the corresponding pyridine derivatives (**5a** and **5c**). Azinesulfonyl chlorides **5a**, **5c**, **5d** and **5f** were too unstable to be isolated and stored in the pure state, as they underwent decomposition to sulfur dioxide and the respective chloroazines. However, immediately after the synthesis, compounds **5a**, **5c**, **5d** and **5f** could be extracted with cold (0 °C) deuterochloroform, and fully characterized (at 10 °C, up to 1 h) with ^{1}H and ^{13}C NMR spectra, which exhibited substituent effects (Δδ) typical for chlorosulfonyl group observed for other isomers of chlorosulfonylazines (**5**). Additionally, both NMR spectra showed that content of compounds **5a**, **5c**, **5d** and **5f** in $CDCl_3$ solution ranged from 90 up to 95 % (or 99 % for **5a**) contaminated with the respective chloropyridine or chloroquinoline (**1**). Azinesulfonyl chlorides (**5a**, **c**, **d** and **f)** were successfully converted to the respective azinesulfonamides (**6a**, **c**, **d** and **f**).

The structure of all thioazine derivatives (**2**, **4**, **5** and **6**) were proved by ^{1}H NMR spectral data and mp's of our products fit well the literature data of all known compounds except 7-quinolinesulfonic acid derivatives (**5i** and **6i**) mentioned in the old papers of Claus.[36]

CONCLUSIONS

Our results (collected in Table) supplemented by corresponding literature data (mentioned as *sub-scripts* to the Table) prove that both types of azinesulfonyl chlorides (**5**) with chlorosulfonyl group in *non-aza*-activated position **5**(**b**, **e**, **g**, **h**, **i**, **j**, **k**) and *aza*-activated position **5**(**a**, **c**, **d**, **f**) are available as isolable compounds by oxidative chlorination of the respective thioazines (**3**) or (**4**), which allows to omit the stage of isolation of azinethiol (**3**) and azinesulfonic acid for *non-aza*-activated isomers. This approach is advantageous over the method of the Barrett's group,[37] for formation of azinesulfonyl chloride in the reaction of azinemetallic derivatives with sulfuryl chloride, which makes even the isolation of crude azinesulfonyl chloride very difficult or impossible and, moreover, may reduce the application of these azinesulfonyl chlorides to couple with the molecules of biologically active compounds.

Close approach concerning mainly α-pyrimidine- and α-pyridinesulfonyl chlorides and fluorides based on the oxidation of azinethiols with hypochlorite systems has been recently reported.[44]

Key-entry to the synthesis of *non-aza*-activated thioazines isomers (**3**) and (**4**) comes from the reaction of haloazines (**1**) with an excess of sodium methanethiolate as a source of azinethiolates (**3A**), diazinyl disulfides (**4**) or methylthioazines (**2**).

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. All NMR spectra were recorded on a Bruker AVANCE 400 spectrometer operating at 400.22 and 100.64 MHz for ^{1}H and ^{13}C nuclei, respectively, in deuterochloroform or in hexadeuterodimethylsulfoxide solutions with tetramethylsilane (δ 0.0 ppm) as internal standard. The COSY experiments were performed using standard Bruker program. TLC analyses were performed employing Merck's aluminium oxide 60 F_{254} neutral (type E) plates and using a mixture of $CHCl_3$ / EtOH, 10 :1 , v/v as an eluent.

Chloro- and bromoquinolines (**1e**), (**1f**), (**1g**), (**1h**), (**1i**), (**1j**) were obtained by Skraup synthesis.[19] 3-Bromoquinoline (**1d**) and 4-bromoisoquinoline (**1k**) were prepared as described by Kress and Costantino.[38] 3-Bromopyridine (**1b**), 2,2'- bispyridinyl disulfide (**4a**) and 4,4'-bispyridinyl disulfide (**4c**) were commercial products. 2,2'-Bisquinolinyl disulfide (**4d**) and 4,4'-bisquinolinyl disulfide (**4f**) were prepared by oxidation of the respective quinolinethiones with aqueous potassium ferricyanide.[28] Sodium methanethiolate was prepared by dissolving methanethiol (1 mol. eqv.) in cold (-5 ºC) 5 % solution of sodium methoxide (1 mol. eqv.) in methanol under argon atmosphere. The volatile compounds were then evaporated to dryness under vacuum. Potassium methanethiolate was prepared in the same manner.

Reactions of haloazines (**1**) with sodium (or potassium) methanethiolate:

• General procedure A, leading to azinethiolate (**3A**) or crude (non-isolated) azinethiol (**3**).

A mixture of haloazine (**1**) (4 mmol), sodium methanethiolate (1.4 g, 20 mmol) and dry DMF (12 mL) was boiled with stirring under argon atmosphere for 4 h. (The reaction must be carried out in hood as it proceeded with strong evolution of dimethyl sulfide). It was then cooled to 50 °C and the volatile components were evaporated under vacuum from water bath (ca. 70 °C). The residue was dissolved in 5 mL of water and this solution was cooled down in an ice-water bath and then (under argon atmosphere) carefully acidified with 8 mL of 20 % hydrochloric acid. The mixture was again concentrated under vacuum up to 1/3 volume. This residue contains crude (non-isolated) azinethiol and could be used for the preparation of disulfides or azinesulfonyl chlorides as described below.

• Procedure B, leading to methylthioazines (**2**) (Table, entries 7.1 and 8.1)

A mixture of haloazine (**1**) (4 mmol), sodium methanethiolate (0.42 g, 6 mmol) and dry DMF (12 mL) was boiled with stirring under argon atmosphere for 1.5 h and then treated as in procedure A. The residue (after concentration of hydrochloric acid solution) was poured into cold (5 °C) solution of 8.5 % aqueous NaOH (22 mL). The neutral products were extracted with CH_2Cl_2 (3 x 10 mL). The extracts were combined , washed with cold water (2 x 5 mL) and dried with anhydrous sodium sulfate. The solvent was next distilled off and the residue was subjected to TLC analysis which reveals complete consumption of the starting haloazine (**1**). Methylthioazine (**2**) was separated by column chromatography (silicagel 60 / $CHCl_3$).

The aqueous layer contains some amounts of azinethiolate (**3A**) and could either be methylated with methyl iodide (0.12 mL, 2 mmole) to the second portion of methylthioazine (**2**) (isolated by extraction with CH_2Cl_2 as above) or oxidized to disulfide (**4**) as described below.

• Procedure C, demethylation of methylthioazine (**2**) with sodium methanethiolate (Table, entry 5.1)

A mixture of methylthioazine (**2**) (4 mmol), sodium methanethiolate (0.84 g, 12 mmol) and dry DMF

(12 mL) was boiled with stirring under argon atmosphere until the evolution of dimethyl sulfide ceased (*ca*. 1.5 h) and then treated as in procedure A. Azinethiolate (**3A**) was trapped and characterized by methylation (as described above) or by oxidation as presented below.

Procedure D, preparation of diazinyl disulfides (**4**)

A solution of crude azinethiol (**3**) prepared from haloazine (**1**) (general procedure A) or by *S*-demethylation of methylthioazine (**2**) (procedure C) in 8.5 % aqueous NaOH (52 mL) was dropped on stirring at rt during 15 min into 8 % aqueous $K_3Fe(CN)_6$ (260 mL) and then stirred for 15 min. The precipitate of solid disulfides (**4)** was filtered off and finally recrystallized from 50 % aqueous EtOH.

3,3'-Dipyridinyl disulfide (**4b**) was isolated by extraction with $CHCl_3$ (3 x 20 mL), the extracts were dried with anhydrous Na_2SO_4 and then subjected to typical work-up to give oily compound (**4b**) (82 %).

Preparation of azinesulfonyl chloride (**5**) from crude azinethiol (**3A**) (obtained according to procedure A) or from diazinyl disulfide (**4**) (prepared according to procedure D.

Procedure E, chlorination in 80 % AcOH, for isomers with *thio*-substituent in *non-aza*-activated position:

• for diazinyl disulfide (**4**). Gaseous chlorine was passed through a well stirred mixture of diazinyl disulfide (1.8 mmol), 6 mL of $CHCl_3$ and 6 mL of 80 % AcOH cooled at 5 °C at such a rate that temperature was maintained between 15-17 °C. After 15 min. no more heat seemed to be produced. The passage of chlorine was discontinued after 30 min. The mixture was poured into 30 g of ice. The $CHCl_3$ layer was separated, and aqueous layer was extracted with $CHCl_3$ (3 x 5 mL). The $CHCl_3$ extracts were combined, washed with water and dried over. anh. Na_2SO_4. $CHCl_3$ was evaporated to leave semi-solid residue. Crude sulfonyl chlorides (**5**) were used for the preparation of azinesulfonamides (**6**). For analytical purpose azinesulfonyl chlorides (**5**) were recrystallized from light petroleum (or hexane).

• for crude azinethiol (**3**). AcOH (15 mL) was added on cooling to the residue containing crude azinethiol (**3**) (*ca*. 4 mmol) prepared according to procedure A. The mixture was then chlorinated as for diazinyl disulfides (**4**) described above.

Procedure F: chlorination in concentrated hydrochloric acid, applied for all isomers of diazinyl disulfides (**4**) or crude azinethiols (**3**)

• for diazinyl disulfide (**4**). Gaseous chlorine was passed through a well stirred solution of azinyl disulfide (1.8 mmol), conc. hydrochloric acid (6.6 mL) and ice (1.5 g) at -10 °C at such a rate that temperature was maintained between –8 to –10 °C. The passage of chlorine was discontinued after 30 min. The mixture was poured onto ice (17 g) and $NaHCO_3$ (2 g) was added in small portions. The product (solid or oil) was extracted with $CHCl_3$ (or CH_2Cl_2) (3 x 3 mL). Organic layer was washed with ice-cold water (2 x 3 mL) and dried with anhydrous Na_2SO_4. The solvent was distilled off under vacuum. Crude sulfonyl chlorides (**5**) were used for the preparation of azinesulfonamides (**6**).

• for crude azinethiol (**3**): Conc. hydrochloric acid (10 mL) was added on cooling to the residue containing crude azinethiol (ca. 4 mmol) prepared according to procedure A. The mixture was then chlorinated as described above for diazinyl disulfides.

Characterization of α- and γ-azinesulfonyl chlorides (**5a**), (**5c**), (**5d**) and (**5f**)

Compounds **5a**, **5c**, **5d** and **5f** were too unstable to be isolated and stored in the pure state, as they underwent decomposition to sulfur dioxide and the respective chloroazine. However, immediately after the synthesis, they could be extracted with cold (0 °C) $CDCl_3$, and fully characterized (at 10 °C, up to 1 h) with ^{1}H and ^{13}C NMR spectra.

The NMR spectra of compounds **5a**, **5c**, **5d** and **5f** exhibited substitent effects typical for chlorosulfonyl group observed for other isomers of chlorosulfonylazines (**5**). Additionally, both NMR spectra showed, that content of compounds **5a**, **5c**, **5d** and **5f** in $CDCl_3$ solution ranged from 90 up to 99 % contaminated with 5-10 % of the respective chloropyridine or chloroquinoline (**1**).

Synthesis of azinesulfonamides (**6**)

Crude azinesulfonyl chloride (**5**) (2.5 mmol) and conc. NH_4OH (12.5 mL) was stirred at 45 °C for 0.5 h. An excess of ammonia was evaporated under vacuum. Then water was added up to the volume of 10 mL. The solid was filtered off and washed with cold water. It was finally recrystallized from 10 % aqueous EtOH. The best results in the preparation of azinesulfonamides (**6a**, **c**, **d** and **f**) were obtained when a hydrochloric acid solution of azinesulfonyl chlorides (**5a**, **c**, **d** and **f**) (resulted from chlorination-procedure F) was treated with two volumes of conc. NH_4OH at 0 ºC, and then worked-up as above. However, to remove residual chlorine, before amination, the hydrochloric acid solution was kept at water pump vacuum at 0 ºC for 10 min.

5-Methylsulfanylquinoline (**2a**)

pale-yellow oil, lit.,[17] oil. ^{1}H NMR ($CDCl_3$), δ: 2.58 (s, 3H, SCH_3), 7.42-7.45 (m, 2H, H-3 and H-6), 7.63-7.67 (dd, *J* = 8.8, 7.2 Hz, 1H, H-7), 7.91-7.93 (dd, *J* = 8.4, 1.4 Hz, 1H, H-8), 8.60-8.62 (dd, *J* = 8.4, 1.6 Hz, 1H, H-4), 8.91-8.93 (dd, *J* = 4.0 Hz, *J* = 1.6 Hz, 1H, H-2).

6-Methylsulfanylquinoline (**2b**)

mp 43-45 ºC (hexane), lit.,[17] mp 44-46 ºC. ^{1}H NMR ($CDCl_3$): δ= 2.60 (s, 3H, SCH_3), 7.42-7.46 (dd, *J* = 8.4, 4.4 Hz, 1H, H-3), 7.79-7.81 (dd, *J* = 8.8, 1.6 Hz, 1 H, H-7), 7.99-8.00 (m, 2 H, H-5 and H-8), 8.07-8.10 (dd, *J* = 8.4, 1.6 Hz, 1 H, H-4), 8.93-8.95 (dd, *J* = 4.4, 1.6 Hz, 1H, H-2).

3,3'-Bispyridinyl disulfide **(4b)**

pale-yellow oil, b.temp. 180-183 °C/ 4 mm Hg, lit.,[39] b.temp. 155 °C/ 1 mm Hg.

3,3'-Bisquinolinyl disulfide **(4e)**

mp 150-151 °C (EtOH-water), lit.,[17] mp 150-151.5 °C.

5,5'-Bisquinolinyl disulfide **(4g)**

mp 108-109 °C (benzene/hexane), lit.,[17] mp 109 °C.

6,6'-Bisquinolinyl disulfide **(4h)**

mp 118-119 °C (EtOH-water), lit.,[20] 119 °C.

7,7'-Bisquinolinyl disulfide (**4i)**

mp 141-142 °C (EtOH-water). ^{1}H NMR ($CDCl_3$), δ: 7.28-7.39 (dd, *J* = 8.2 Hz, 4.2 Hz, 2H, H-3 and H-3'), 7.69-7.72 (dd, *J* =8.4 Hz, 2.0 Hz, 2H, H-6 and H-6'), 7.78-7.80 (d, *J* = 8.4 Hz, 2H, H-5 and H-5'), 8.11-8.14 (dd, *J* = 8.2 Hz, 1.8 Hz, 2H, H-4 and H-4'), 8.28-8.29 (d, *J* = 2.0 Hz, 2H, H-8 and H-8'), 8.87-8.89 (dd, *J* = 4.2, 1.8 Hz, 2H, H-2 and H-2'). *Anal*. Calcd for $C_{18}H_{12}N_2S_2$ (320.42): C 67.47; H 3.77; N 8.74; S 20.01. Found C 67.30; H 3.69; N 8.61; S 19.77.

4,4'-Bisisoquinolinyl disulfide (**4k)**

mp 135-136 °C (EtOH-water). ^{1}H NMR ($CDCl_3$), δ: 7.62-7.71 (m, 4H, H-6, H-6', H-7 and H-7'), 7.98-8.01 (dd, *J* = 8.2 Hz, 1.2 Hz, 2H, H-5 and H-5'), 8.15-8.17 (dd, *J* = 8.4 Hz, 1.0 Hz, 2H, H-8 and H-8'), 8.44 (s 2H, H-3 and H-3'), 9.20 (s, 2H, H-1 and H-1'). *Anal*. Calcd for $C_{18}H_{12}N_2S_2$ (320.42): C 67.47; H 3.77; N 8.74; S 20.01. Found C 67.27; H 3.70; N 8.84; S 19.79.

2-Pyridinesulfonyl chloride **(5a)**

solid at rt, unstable at rt. ^{1}H NMR ($CDCl_3$), δ: 7.60-7.64 (ddd, *J* = 8.0, 4.8 Hz, 1.2 Hz, 1H, H-5), 7.96-8.01 (ddd, *J* = 8.0, 7.6, 2.0 Hz, 1H, H-4), 8.05-8.07 (dd, *J* = 8.0, 1.2 Hz, 1H, H-3), 8.76-8.77 (dd, *J* = 4.8, 2.0 Hz, 1H, H-6). ^{13}C NMR ($CDCl_3$), δ: 159.2 (C2), 159.0 (C6), 139.4 (C4), 129.5 (C3) 122.2 (C5). Described in the references.[5, 26, 34, 40]

3-Pyridinesulfonyl chloride **(5b)**

colourless oil, lit.,[40] oil. ^{1}H NMR ($CDCl_3$), δ; 7.70-7.74 (dd, *J* = 7.6, 4.8 Hz, 1H, H-5), 8.43-8.45 (dd, *J* = 7.6, 2.0 Hz, 1H, H-4), 9.03-9.05 (dd, *J* = 4.8, 2.0 Hz, 1H, H-6), 9.31-9.32 (d, *J* = 2.0 Hz, 1H, H-2). Bruice and co-workers[43] reported mp and ^{1}H NMR spectrum of hydrochloride of 3-pyridinesulfochloride instead of the respective data of parent compound (**5b**).

4-Pyridinesulfonyl chloride (**5c**)

Isolated only in the form of methylene chloride or chloroform solutions, unstable at 10 °C, decomposition observed within 1 h. ^{1}H NMR ($CDCl_3$), δ: 7.86-7.88 (ddd, *J* = 4.5, 1.6, 0.3 Hz, 2H, H-3 and H-5), 8.99-9.01 (ddd, *J* = 4.5, 1.6, 0.3 Hz, 2H, H-2 and H-6). ^{13}C NMR ($CDCl_3$), δ: 119.6 (C3 and C5), 151.6 (C4), 152.2 (C2 and C6). Described in the reference.[34]

2-Quinolinesulfonyl chloride (**5d)**

Solid at rt, unstable at rt. ^{1}H NMR ($CDCl_3$), δ: 7.79-7.83 (ddd, *J* = 8.8, 7.0, 0.9 Hz, 1H, H-6), 7.92-7.96 (ddd, *J* = 8.8, 7.0, 1.2 Hz, 1H, H-7), 7.99-8.01 (d, *J* = 8.4 Hz, 1H, H-3), 8.14-8.16 (dd, *J* = 8.8, 0.9 Hz, 1H, H-5), 8.32-8.34 (dd, *J* = 8.8, 1.2 Hz, 1 H, H-8), 8.52-8.54 (d, *J* = 8.4 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$), δ: 117.0 (III^o), 128.2 (III^o), 130.1 (C4a), 130.8 (2 x III^o), 132.5 (III^o), 140.2 (III^o), 139.0 (C4), 147.3 (C8a), 158.1 (C2). Described in the reference.[5]

3-Quinolinesulfonyl chloride **(5e)**

mp 96-97 ^{o}C (hexane), lit.,[26] mp 85-87 ^{o}C, mentioned as a part of sample collection.[4] ^{1}H NMR ($CDCl_3$), δ: 7.81-7.85 (ddd, *J* = 8.0, 7.2, 1.4 Hz, 1H, H-6), 8.03-8.06 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H, H-7), 8.07-8.10 (dd, *J* = 8.0, 1.6 Hz, 1 H, H-5), 8.34-8.36 (dd, *J* = 8.4, 1.4 Hz, 1H, H-8), 8.94-8.95 (d, *J* = 2.0 Hz, 1H, H-4), 9.44-9.45 (d, *J* = 2.0 Hz, 1H, H-2).

4-Quinolinesulfonyl chloride **(5f)**

Isolated only in the form of methylene chloride or chloroform solutions, unstable at 10 ^{o}C, within 1 h. ^{1}H NMR ($CDCl_3$), δ: 8.00-8.04 (dd, *J* = 8.8, 7.6 Hz, 1H, H-6), 8.08-8.09 (d, *J*=6.0 Hz, 1H, H-3), 8.14-8.18 (dd, *J* = 8.4, 7.6 Hz, 1H, H-7), 8.47-8.49 (d, *J* = 8.4 Hz, 1H, H-8), 8.91-8.93 (d, *J* = 8.8 Hz, 1H, H-5), 9.15-9.16 (d, *J* = 6.0 Hz, 1H, H-2). ^{13}C NMR ($CDCl_3$), δ: 122.3 (C3), 122.9 (C6), 125.5 (C5), 127.5 (C4a), 131.6 (C7),136.0 (C8), 139.0 (C4), 143.13 (C8a), 153.5 (C2). Mentioned in the reference[26] as a compound with mp 109-111 ºC, which temperature is not possible to be reached without compound decomposition according to our studies.

5-Quinolinesulfonyl chloride **(5g)**

mp 91-92 ^{o}C (hexane), lit.,[17] mp 91-95 ^{o}C. ^{1}H NMR ($CDCl_3$), δ: 8.16-8.22 (m, 2H, H-3 and H-7), 8.69-8.70 (dd, *J* = 7.2, 1.4 Hz, 1H, H-6), 9.25-9.29 (m, 2H, H-4 and H-8), 9.69-9.71 (dd, *J* =4.4, 1.2 Hz, 1H, H-2).

6-Quinolinesulfonyl chloride (**5h)**

mp 89-90 ^{o}C (hexane), lit.,[20] mp 91 ^{o}C. ^{1}H NMR ($CDCl_3$), δ: 7.62-7.66 (dd, *J* = 8.3, 4.2 Hz, 1H, H-3), 8.23-8.26 (dd, *J* = 9.0, 2.2 Hz, 1H, H-7), 8.33-8.35 (d, *J* = 9.0 Hz, 1H, H-8), 8.37-8.39 (dd, *J*=8.3, 1.6 Hz, 1H, H-4), 8.61-8.62 (d, *J* = 2.2 Hz, 1H, H-5), 9.14-9.15 (dd, *J* = 4.2, 1.6 Hz, 1H, H-2).

7-Quinolinesulfonyl chloride **(5i)**

mp 115-116 ^{o}C (hexane). ^{1}H NMR ($CDCl_3$), δ: 7.68-7.71 (dd, *J* = 8.4, 4.4 Hz, 1H, H-3), 8.10-8.16 (m, 2H, H-5 and H-6), 8.35-8.37 (dd, *J* = 8.4, 1.6 Hz, 1H, H-4), 8.92-8.93 (d, *J* = 1.6 Hz, 1H, H-8), 9.14-9.15 (dd, *J* = 4.4, 1.6 Hz, 1H, H-2). *Anal.* Calcd for $C_9H_6ClNO_2S$ (227.66): C 47.48; H 2.66; N 6.15; S 14.08. Found C 47.28; H 2.46; N 6.01; S 13.78.

8-Quinolinesulfonyl chloride **(5j)**

mp 130-131 °C (hexane), lit.,[17] mp 131 °C. ^{1}H NMR ($CDCl_3$), δ: 7.63-7.66 (dd, *J* = 7.6, 4.4 Hz, 1H, H-3), 7.68-7.72 (dd, *J* = 8.4, 8.0 Hz, 1H, H-6) 8.22-8.24 (dd, *J* = 8.0, 1.6 Hz, 1H, H-5), 8.31-8.33 (dd, *J* = 8.4, 1.6 Hz, 1H, H-7), 8.53-8.56 (dd, *J* = 7.6, 1.6 Hz, 1H, H-4), 9.23-9.25 (dd, *J* = 4.4, 1.6 Hz, 1H, H-2).

4-Isoquinolinesulfonyl chloride **(5k)**

mp 112-113 °C (hexane). ^{1}H NMR ($CDCl_3$), δ: (ddd, *J* = 8.0, 7.2, 1.4 Hz, 1H, H-6), 7.98-8.03 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H, H-7), 8.30-8.32 (dd, *J* = 8.0, 1.6 Hz, 1H, H-5), 8.75-8.77 (dd, *J* = 8.4, 1.4 Hz, 1H, H-8), 9.25 (s, 1H, H-3), 9.69 (s, 1H, H-1). *Anal.* Calcd for $C_9H_6ClNO_2S$ (227.66): C 47.48; H 2.66; N 6.15; S 14.08. Found C 47.23; H 2.60; N 5.95; S 13.81.

2-Pyridinesulfonamide **(6a)**

mp 140-141 °C (EtOH-water), lit.[34] mp 133 °C. ^{1}H NMR (DMSO-d_6), δ: 7.46 (s, 2H, NH_2), 7.62-7.65 (ddd, *J* = 7.6, 4.8, 1.6 Hz, 1H, H-5), 7.92-7.95 (dd, *J* = 8.0, 1.6 Hz, 1H, H-3), 8.05-8.09 (ddd, *J* = 8.0, 7.6, 1.6 Hz, 1H, H-4), 8.71-8.72 (dd, *J* = 4.8, 1.6 Hz, 1H, H-6).

3-Pyridinesulfonamide (**6b)**

mp 109-110 °C (hexane-acetone), lit.,[41] mp 110-111 °C. ^{1}H NMR (DMSO-d_6), δ: 7.61 (s, 2H, NH_2), 7.62-7.65 (dd, *J* = 8.0, 4.8 Hz, 1H, H-5), 8.18-8.20 (dd, *J* = 8.0, 1.6 Hz, 1H, H-4), 8.78-8.80 (dd, *J* = 4.8, 1.6 Hz, 1H, H-6), 8.98-8.99 (d, *J* = 1.6 Hz, 1H, H-2).

4-Pyridinesulfonamide **(6c)**

mp 168-169 °C (water), lit.,[34] mp 168-169 °C. ^{1}H NMR (DMSO-d_6), δ: 7.70 (s, 2H, NH_2), 7.74-7.75 (dd, *J* = 4.4, 1.6 Hz, 2H, H-3 and H-5), 8.82-8.84 (dd, *J* = 4.4, 1.6 Hz, 2H, H-2 and H-6).

2-Quinolinesulfonamide **(6d)**

mp 164-165 °C (EtOH-water). ^{1}H NMR (DMSO-d_6), δ: 7.64 (s, 2 H, NH_2), 7.76-7.80 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, H-6), 7.90-7.94 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H, H-7), 8.02-8.04 (d, *J* = 8.8 Hz, 1H, H-3), 8.12-8.14 (m, 2H, H-5 and H-8), 8.66-8.68 (d, *J* = 8.8 Hz, 1H, H-4). *Anal.* Calcd for $C_9H_8N_2O_2S$ (208.33): C 51.91; H 3.87; N 13.45; S 15.40. Found C 51.86; H 3.89 N 13.11; S 15.27.

3-Quinolinesulfonamide (**6e)**

mp 204-205 °C (EtOH-water). ^{1}H NMR (DMSO-d_6), δ: 7.67 (s, 2H, NH_2), 7.72-7.76 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H, H-6), 7.90-7.94 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H, H-7), 8.11-8.13 (dd, *J* = 8.0, 1.4 Hz, 1H, H-5), 8.20-8.22 (dd, *J* = 8.4, 1.2 Hz, 1H, H-8), 8.83-8.84 (d, *J* = 2.4 Hz, 1H, H-4), 9.22-9.23 (d, *J* = 2.4 Hz, 1H, H-2). *Anal.* Calcd.for $C_9H_8N_2O_2S$ (208.33): C 51.91; H 3.87; N 13.45; S 15.40. Found C 51.80; H 3.86; N 13.29; S 15.2.

4-Quinolinesulfonamide (**6f)**

mp 184-185 °C (EtOH-water). ^{1}H NMR (DMSO-d_6), δ: 7.77-7.81 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H, H-6), 7.88-7.92 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1H, H-7), 7.96-7.97 (d, *J* = 4.4 Hz, 1H, H-3), 8.00 (s, 2H, NH_2), 8.17-8.19 (dd, *J* = 8.0, 1.2 Hz, 1H, H-5), 8.61-8.63 (dd, *J* = 8.4, 1.2 Hz, 1H, H-8), 9.11-9.12 (d, *J* = 4.8 Hz, 1H, H-2). *Anal.* Calcd. for $C_9H_8N_2O_2S$ (208.33): C 51.91; H 3.87; N 13.45; S 15.40. Found C 51.90; H 3.86 N; 13.09; S 15.23.

5-Quinolinesulfonamide **(6g)**

mp 177-178 °C (EtOH-water). ^{1}H NMR (DMSO-d_6), δ: 7.71-7.75 (dd, *J* = 8.4, 4.4 Hz, 1H, H-3), 7.79 (s, 2H, NH_2), 7.88-7.92 (dd, *J* = 8.4, 7.2 Hz, 1H, H-7), 8.19-8.22 (dd, *J* = 7.2, 1.2 Hz, 1H, H-6), 8.26-8.28 (dd, *J* = 8.4, 1.2 Hz, 1H, H-8), 9.01-9.03 (dd, *J* = 8.4, 1.2 Hz, 1H, H-4), 9.04-9.05 (dd, *J* = 4.4, 1.2 Hz, 1H, H-2). *Anal.* Calcd. for $C_9H_8N_2O_2S$ (208.33): C 51.91; H 3.87; N 13.45; S 15.40. Found C 51.79; H 3.83 N; 13.29; S 15.27.

6-Quinolinesulfonamide (**6h)**

mp 191-192 °C (EtOH-water), lit.,[20] mp 192 °C. ^{1}H NMR (DMSO-d_6), δ: 7.56 (s, 2H, NH_2), 7.65-7.69 (dd, *J* = 8.4, 4.4 Hz, 1H, H-3), 8.01-8.14 (dd, *J* = 8.8, 2.0 Hz, 1H, H-7), 8.19-8.20 (d, *J* = 8.8 Hz, 1H, H-8), 8.48-8.49 (d, *J* = 2.0 Hz, 1H, H-5), 8.59-8.60 (dd, *J* = 8.4, 1.6 Hz, 1H, H-4), 9.02-9.04 (dd, *J* = 4.4, 1.6 Hz, 1H, H-2).

7-Quinolinesulfonamide **(6i)**

mp 192-193 °C (EtOH-water). ^{1}H NMR (DMSO-d_6), δ: 7.60 (s, 2H, NH_2), 7.68-7.71 (dd, *J* = 8.4, 4.0 Hz, 1H, H-3), 7.96-7.99 (dd, *J* = 8.6, 1.8 Hz, 1H, H-6), 8.19-8.21 (d, *J* = 8.6 Hz, 1H, H-5), 8.44-8.45 (d, *J* = 1.8 Hz, 1H, H-8), 8.48-8.50 (dd, *J* = 8.4, 1.6 Hz, 1H, H-4), 9.04-9.05 (dd, *J* = 4.0, 1.6 Hz, 1H, H-2). $C_9H_8N_2O_2S$ (208.23): calcd. C 51.91; H 3.87; N 13.45; S 15.40; found C 51.90; H 3.86 N 13.18; S 15.18.

8-Quinolinesulfonamide **(6j)**

mp 183-184 °C (EtOH-water), lit.,[42] mp 179 °C. ^{1}H NMR (DMSO-d_6), δ: 7.36 (s, 2H, NH_2), 7.69-7.77 (m, 2H, H-3 and H-6), 8.25-8.28 (dd, *J* = 8.4, 1.4 Hz, 1H, H-5), 8.29-8.30 (dd, *J* = 7.2, 1.4 Hz, 1H, H-7), 8.53-8.55 (dd, *J* = 8.4, 1.6 Hz, 1H, H-4), 9.06-9.08 (dd, *J* = 4.4, 1.6 Hz, 1H, H-2).

4-Isoquinolinesulfonamide **(6k)**

mp 248-249 °C (EtOH-water). ^{1}H NMR (DMSO-d_6), 7.84-7.87 (m, 3H, H-6 and NH_2), 7.98-8.03 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H, H-7), 8.31-8.33 (dd, *J* = 8.4, 1.6 Hz, 1H, H-5), 8.59-8.61 (dd, *J* = 8.4, 1.4 Hz, 1H, H-8), 8.98 (s, 1H, H-3), 9.55 (s, 1H, 1-H). *Anal.* Calcd for $C_9H_8N_2O_2S$ (208.23): C 51.91; H 3.87; N 13.45; S 15.40. Found C 51.66; H 3.93; N 13.36; S 15.21.

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