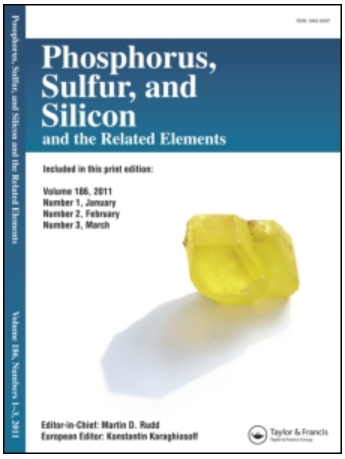


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Pyridazine Derivatives and Related Compounds, Part 28.[1] Pyridazinesulfonamides: Synthesis and Antimicrobial Activity

Fatma El-Mariah[a]; Ekhlass Nassar[a]; Mona Hosny[a]; Ali Deeb[b]
[a] Department of Chemistry, Faculty of Girls, Ain Shams University, Cairo, Egypt [b] Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt

To cite this Article El-Mariah, Fatma , Nassar, Ekhlass , Hosny, Mona and Deeb, Ali(2009) 'Pyridazine Derivatives and Related Compounds, Part 28.[1] Pyridazinesulfonamides: Synthesis and Antimicrobial Activity', Phosphorus, Sulfur, and Silicon and the Related Elements, 184: 1, 92 — 102
To link to this Article: DOI: 10.1080/10426500802080246
URL: http://dx.doi.org/10.1080/10426500802080246

Phosphorus, Sulfur, and Silicon, 184:92–102, 2009

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802080246

Taylor & Francis
Taylor & Francis Group

Pyridazine Derivatives and Related Compounds, Part 28.[1] Pyridazinesulfonamides: Synthesis and Antimicrobial Activity

Fatma El-Mariah,[1] Ekhlass Nassar,[1] Mona Hosny,[1] and Ali Deeb[2]
[1]Department of Chemistry, Faculty of Girls, Ain Shams University, Cairo, Egypt
[2]Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt

*The reaction of 3-chloropyridazine **1** with N –(un)Substituted 4-aminosulfonamides **3** gave the 3-substituted aminopyridazines **4**. Also In addition, pyridazine-3-sulfonamides **7** were prepared from the reaction of pyridazine-3-sulfonylchloride **6** with different amines. All of these derivatives have been characterized by analytical and spectroscopic studies, and also were tested for their in vitro antibacterial and antifungal activity against a variety of microorganisms.*

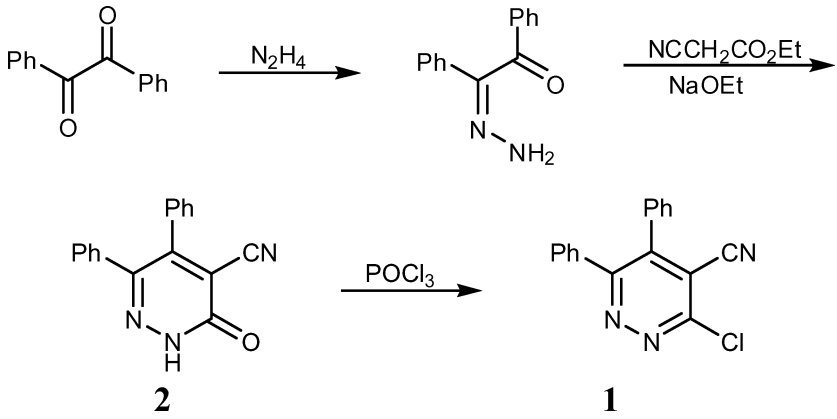
Keywords 3-Substituted aminopyridazines; N-substituted pyridazine-3-sulfonamides

INTRODUCTION

Many pyridazines exhibit biological activity and some are used as drugs.[2,3]

In the last few years our group has been interested in the synthesis of pyridazine derivatives with potential biological activity, and we have published several articles on this subject. On the other hand, the sulfonamides group form the bioactive moiety of many compounds with therapeutical interest, such as antibacterials, diuretics, antidiabetics, and antibiotics.[4] For these reasons, we are interested in continuing our work in this area[5] to produce new pyridazine derivatives containing sulfamoyl moiety and study their antibacterial and antifungal properties.

Received 11 December 2007; accepted 11 February 2008.
The author A.D. acknowledges the help of Quality Control and Propagation of Plants, Department of Botany, Faculty of Girls, Ain Shams University for carrying out the antimicrobial activity.
Address correspondence to Ali Deeb, Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt. E-mail: dralideeb@hotmail.com



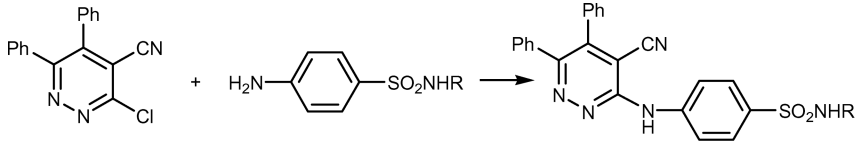
2 **1**

SCHEME 1

RESULTS AND DISCUSSION

Compounds were obtained as illustrated in Scheme 1, starting with 3-chloro-5,6-diphenylpyridazine-4-carbonitrile **1**. The method utilized for the synthesis of **1** is outlined in Scheme 2. The necessary benzil and benzilmonohydrazone were commercially available or easily prepared by following previously described methods.[6] The desired pyridazinone has been obtained by the reaction of benzilmonohydrazone with ethyl cyanoacetate and sodium ethoxide.[7] Compound **2** was transformed into **1** by treatment with phosphorus oxychloride.[8]

The N^1-(un)substituted 4-aminobenzenesulfonamides **3** were prepared using a previously described method.[9] The spectroscopic characterization and analysis are shown in the Experimental section.



1 **3a-i** **4a-i**

4a, R = H
b, R = n-Pr
c, R = CH_2Ph
d, R = NHPh
e, R = Ph
f, R = C_6H_4 Me *(p-)*
g,R = C_6H_4 OMe*(p-)*
h, R = C_6H_4 Cl *(p-)*
i, R = C_6H_4 NO *(p-)*

SCHEME 2

TABLE I Physical and Spectroscopic Data of N^1-Substituted 4-Aminobenzenesulfonamides 3

Compound No.	R	Color	M.p. (°C)	Yield (%)	IR (kBr) γ max cm^{-1}
3a	H	Color less	161–162	90	
3b	n-Pr	Color less	158–159	70	3435, 3251, 3036, 2949, 1640, 1307, 1151
3c	CH_2Ph	Brown	167–168	90	3400, 3336, 3263, 3012, 2958, 1646, 1319, 1151
3d	NHPh	Color less	60–61	70	3470, 3376, 3236, 3059, 2969, 1623, 1309, 1150
3e	Ph	Color less	180–181	85	3410, 3340, 3120, 3040, 1639, 1329, 1150
3f	C_6H_4Me (*p*-)	Color less	186–187	80	3413, 3343, 3125, 3046, 2918, 1636, 1321, 1153
3g	C_6H_4OMe (*p*-)	Color less	182–183	95	3486, 3397, 3263, 1632, 1318, 1150
3h	C_6H_4Cl (*p*-)	Pale yellow	178–179	80	3412, 3344, 3108, 1633, 1315, 1153
3i	$C_6H_4NO_2$ (*p*-)	Yellow	112–113	65	3491, 3389, 3299, 3093, 1628, 1343, 1152

The nucleophilic substitution of the 4-amino group of **3** with the 3-chloro group of compound **1** yielded the corresponding 3-substituted aminopyridazines $\mathbf{4}_{a-i}$. The structure of the synthesized compounds was established on the basis of their IR, and mass spectral studies. Physical and analytical data of compounds **3** and **4** are given in Tables I–III.

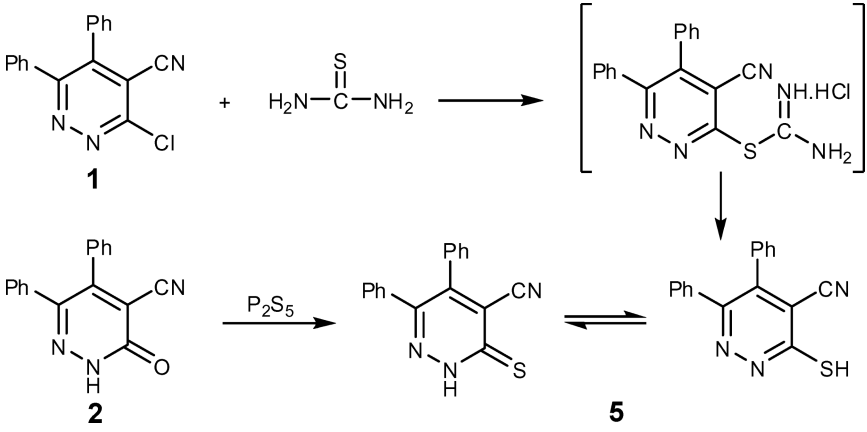
As an extension of our studies, we have been interested in preparing the interesting sulfonamide derivatives in which the sulfur atom is joined directly to a carbon of the pyridazine ring. They have usually been prepared via an alternate route starting from the 3-mercaptopyridazine derivative. Thus, when compound **1** was allowed to react with ethanolic thiouronium, salt in 90 % yield was obtained, which on hydrolysis with 2.5 N sodium hydroxide followed by acidification with hydrochloric acid (pH 6), gave 4-cyano-5,6-diphenylpyridazine-3(2H)-thione **5**.[10] The structure of **5** was inferred from microanalytical data and by comparison with the product obtained by the action of phosphorus pentasulphide on **2** (Scheme 3).

The precursor pyridazine-3-chlorosulfonyl was synthesized similar to the literature procedure.[11] The low temperature oxidative chlorination of thiopyridazine **5** gave the corresponding sulfonyl chloride **6**. Because of the instability of the sulfonyl choride, the crude product was

TABLE II Spectral Data of 3-Substituted Aminopyridazines 4

Compound No.	IR (KBr) cm^{-1}	Ms (m/z, %)
4a	3266, 3127, 3062, 2228, 1663, 1329, 1157	427 (M^+, 00), 363 (50), 345 (50), 244 (24), 214 (53)
4b	3239, 3180, 3060, 2939, 2222, 1660, 1332, 1152	469 (M^+, 11), 411 (7), 347 (28), 273 (100)
4c	3440, 3291, 2225, 1666, 1406, 1155	517 (M^+, 15), 516 (14), 490 (14), 411 (17), 273 (19)
4d	3361, 3057, 2225, 1666, 1406, 1153	516 (M^+- 2,8), 515 (29), 504 (22), 503 (29), 380 (65), 379 (100)
4e	3351, 3251, 3062, 2229, 1664, 1320, 1156	504 (M^++ 1,28), 503 (69), 411 (22), 347 (100)
4f	3380, 3289, 3053, 2920, 2227, 1598, 1329, 1154	517 (M^+, 21), 263 (17), 349 (77), 348 (91), 269 (3), 244 (10), 106 (100)
4g	3407, 3291, 3060, 2996, 2229, 1596, 1330, 1154	533 (M^+, 19), 454 (4), 347 (10), 122 (100)
4h	3290, 3133, 3064, 2227, 1597, 1330, 1156, 700	538 (M^+, 26), 412 (4), 382 (47) 381 (98), 347 (100)
4i	3330, 3234, 3058, 2232, 1666, 1529, 1342, 1156	548 (M^+, 28), 499 (35), 393 (39), 392 (84), 347 (100)

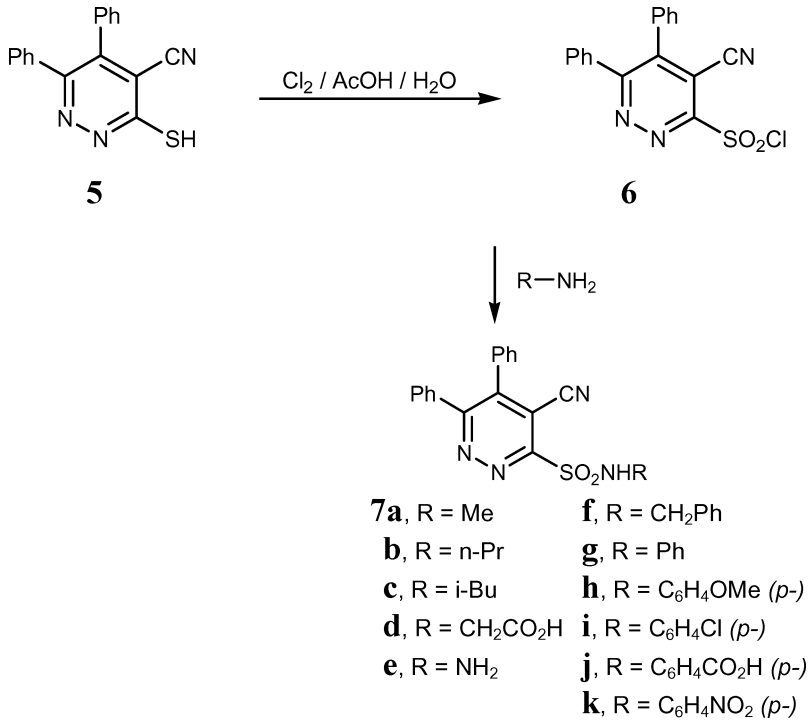
usually converted directly to the more stable sulfonamides $\mathbf{7}_{a-k}$ by the action of amines (Scheme 4). The structure of compounds **7** was established on the basis of their IR, ^{1}H-NMR, and mass spectral studies. Physical and analytical data are given in Tables IV and V.



SCHEME 3

TABLE III Physical and Analytical Data of 3-Substituted Aminopyridazines 4

Compound	R	Color	m.p. (°C)	Yield (%)	Molecular formula	Elemental analysis (%), found (calc)		
						C	H	N
4a	H	Pale yellow	228–230	80	$C_{23}H_{17}N_5O_2S$	64.30 (64.62)	3.90 (4.01)	16.10 (16.38)
4b	n-Pr	Pale yellow	240–242	95	$C_{26}H_{23}N_5O_2S$	66.30 (66.50)	4.80 (4.94)	14.70 (14.92)
4c	CH_2Ph	Pale yellow	225–226	85	$C_{30}H_{23}N_5O_2S$	69.30 (69.61)	4.20 (4.48)	13.20 (13.53)
4d	NHPh	Brown	111–112	80	$C_{29}H_{22}N_6O_2S$	67.00 (67.16)	4.00 (4.20)	15.90 (16.21)
4e	Ph	Pale yellow	188–189	88	$C_{29}H_{21}N_5O_2S$	68.90 (69.17)	4.00 (4.20)	13.70 (13.91)
4f	C_6H_4Me (*p*-)	Pale yellow	193–194	85	$C_{30}H_{23}N_5O_2S$	69.30 (69.61)	4.50 (4.48)	13.30 (13.53)
4g	C_6H_4OMe (*p*-)	Yellow	219–220	88	$C_{30}H_{23}N_5O_3S$	67.40 (67.52)	4.20 (4.34)	13.00 (13.13)
4h	C_6H_4Cl (*p*-)	Pale yellow	226–228	90	$C_{29}H_2O\ C_1\ N_5O_2S$	64.50 (64.74)	3.50 (3.75)	12.90 (13.02)
4i	$C_6H_4NO_2$ (*p*-)	Pale yellow	212–214	95	$C_{29}H_{20}N_6O_4S$	63.20 (63.49)	3.40 (3.68)	15.10 (15.32)



SCHEME 4

Screening for Antimicrobial and Antifungal Activity: Experimental Procedure

The preliminary antimicrobial activity of the synthesized derivatives was determined in vitro by the filter paper disc method.[12] Four bacterial isolates (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Bacillus subtilis*) and two fungal isolates (*Candida albicans* and *Asperggillus niger*) were used as test organisms. The culture media were normal nutrient agar for bacteria, and *Sabouraud* dextrose agar for *Candida spp*. and *Asperggillus niger*. Filter paper discs (7.0 mm diameter) punched from No.1 Whatman filter paper were sterilized by autoclaving followed by drying at 40°C for 1 h. They were then impregnated with 50 μg/ml tested compound in dimethylformamide (DMF). The sterile medium was inoculated onto the surface with the test organism so that each 100 mL of the medium received 1 mL of a 24-h old culture of the bacterium or 3-day-old culture of spore suspension of the fungus. After the inoculum had dried, the dried discs were placed on the medium. A control disc (DMF) was also placed onto the medium.

TABLE IV Spectral Data of N-Substituted 4-Cyano-5,6-diphenylpyridazine-3-sulfonamides 7

Compound No.	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6) δ ppm	Ms (m/z_1 %)
7a	3234, 3059, 2920, 2340, 1676, 1444, 1326, 1124	13.4 (s, 1H, NH), 8.1–7.03 (m, 10H, 2Ph), 2.44 (d, 3H, CH_3)	—
7b	3375, 3058, 2928, 2290, 1677, 1443, 1379, 1152		383 (M^+ + 5,61), 358 (52), 340 (19), 312 (26), 290 (39), 178 (100)
7c	3147, 3058, 2961, 2292, 1654, 1443, 1384, 1182		391 (M^+ −1.4), 383 (3), 346 (2), 311 (5), 290 (100), 288 (7), 275 (8)
7d	3400 (br), 3157, 3059, 2342, 1670, 1378, 1125		394 (M^+, 0.3), 392 (0.3), 388 (0.4), 290 (100), 247 (14), 218 (14), 139 (10)
7e	3242, 3141, 3057, 2340, 1655, 1400, 1105		351 (M^+, 1.1), 293 (2), 279 (2), 256 (3), 217 (3), 179 (5), 149 (35), 69 (100)
7f	3406, 3364, 3055, 3028, 2341, 1657, 1445, 1357, 1180	13.4 (s, 1H, NH), 7.95–7.02 (m, 15H, 3Ph), 2.5 (s, 2H, CH_2)	347 (4), 386 (12), 380 (37), 334 (100), 262 (24), 232 (10), 178 (32)
7g	3376, 3056, 2281, 1399, 1178		411 (M^+, 1), 365 (2), 347 (1.6), 290 (3), 182 (38), 151 (14), 126 (10), 77 (100)
7h	3419, 3091, 2929, 2838, 2278, 1605, 1509, 1445, 1299, 1175	13.6 (s, 1H, NH), 7.60–7.00 (m, 14H, phenyl protons), 3.80 (s, 3H, OCH_3)	439 (3), 395 (100), 378 (29), 350 (22), 290 (30), 216 (10)
7i	3372, 3058, 2276, 1654, 1300, 1176		446 (M^+, 0.4), 399 (9), 384 (25), 383 (37), 324 (4), 291 (31), 290 (57), 178 (100)
7j	3460, 3364, 3057, 2923, 2342, 1677, 1601, 1513, 1315, 1173		457 (M^+ + 1,3), 456 (M^+, 4), 424 (4), 407 (5), 393 (5), 239 (11), 208 (11), 193 (15), 178 (14), 136 (100)
7k	3480, 3362, 3076, 2221, 1629, 1545, 1181		457 (M^+, 0.1), 450 (0.7), 411 (42), 410 (100), 393 (14), 365 (13), 216 (15), 214 (13), 189 (52)

TABLE V Physical and Analytical Data of N-Substituted 4-Cyano-5, 6-diphenylpyridazine-3-sulfonamides 7

Compound No.	R	Color	M.p. (°C)	Yield (%)	Molecular formula	Elemental analysis (%), found (calc.)		
						C	**H**	**N**
7a	Me	Brownish yellow	128–130	82	$C_{18}H_{14}N_4O_2S$	61.40 (61.70)	3.90 (4.03)	15.80 (15.99)
7b	n-Pr	Brown	142–143	85	$C_{20}H_{18}N_4O_2S$	63.20 (63.47)	4.60 (4.79)	14.60 (14.80)
7c	i-Bu	Light brown	123–124	80	$C_{21}H_{20}N_4O_2S$	64.00 (64.26)	4.90 (5.14)	14.00 (14.28)
7d	CH_2CO_2H	Yellow	124–125	90	$C_{19}H_{14}N_4O_4S$	57.50 (57.86)	3.20 (3.58)	14.00 (14.21)
7e	NH_2	Brown	130–131	80	$C_{17}H_{13}N_5O_2S$	58.00 (58.11)	3.40 (3.73)	19.80 (19.93)
7f	CH_2Ph	Light brown	178–180	75	$C_{24}H_{18}N_4O_2S$	67.20 (67.59)	4.00 (4.25)	12.90 (13.14)
7g	Ph	Brown	144–146	82	$C_{23}H_{16}N_4O_2S$	66.80 (66.97)	3.80 (3.91)	13.40 (13.58)
7h	C_6H_4OMe (*p*-)	Brown	126–127	80	$C_{24}H_{18}N_4O_3S$	65.00 (65.14)	3.80 (4.10)	12.30 (12.66)
7i	C_6H_4Cl (*p*-)	Brown	125–126	85	$C_{23}H_{15}ClN_4O_2S$	61.90 (61.81)	3.30 (3.38)	12.30 (12.54)
7j	$C_6H_4CO_2H$ (*p*-)	Brown	138–139	85	$C_{24}H_{16}N_4O_4S$	63.00 (63.13)	3.40 (3.53)	12.00 (12.27)
7k	$C_6H_4NO_2$ (*p*-)	Brown	100–101	90	$C_{23}H_{15}N_5O_4S$	60.50 (60.38)	3.10 (3.30)	15.40 (15.31)

TABLE VI Antibacterial and Antifungal Activity

No.	Esch. coli	Pseud. aerugin	Staph. aureus	Bacillus subtilis	Candida albicans	Asp. niger
4a	++	−	−	−	−	−
4b	++	++	−	−	−	−
4c	+++	−	−	−	−	−
4d	++	−	++	++	−	−
4e	++	−	−	−	−	−
4f	++	−	++	++	−	−
4g	++	−	−	−	−	−
4h	−	−	−	++	−	−
4i	++	−	−	−	−	−
7a	+++	−	++	−	−	−
7b	+++	−	−	++	−	−
7c	+++	−	++	++	−	−
7d	−	−	++	+++	−	−
7e	+++	−	++	+++	−	−
7f	+++	−	++	++	−	−
7g	−	−	+++	+++	−	−
7h	−	−	+++	+++	−	−
7i	+++	−	−	++	−	−
7j	+++	+++	++	−	−	−
7k	−	−	++	++	−	−
Cipr	+++	+++	+++	+++	−	−
Nys	−	−	−	−	+++	−

Zone of inhibition: +++ = 25–30 mm; ++ = 15–20 mm; − = negative inhibition.

The plates were incubated at 37°C, and the resulting inhibition zones were measured. The screening results are given in Table VI.

RESULTS

As revealed from the results, most of the synthesized compounds showed antibacterial activity. The most toxic compounds against bacterial isolates were compounds **4c, 7a, 7b, 7c, 7d, 7e, 7f, 7g, 7h, 7i,** and **7j**.

The test microorganisms were less sensitive to compounds **4a, 4b, 4d, 4e, 4f, 4g, 4h, 4i**, and **7k**.

These compounds were slightly effective only on *Pseudomonas Aeruginosa.*

All compounds did not exert inhibition zone against fungal isolates. From these results, we can conclude that the biologically active

compounds are nearly as active as standard antibiotic Ciprofloxacin and less active than the fungicide Nystin.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on a BRUKER Vector 22 Germany spectrometer (KBr) (Germany). The ^{1}H-NMR spectra were obtained on Varian Gemini 200 MHz spectrometer (USA), and chemical shifts are expressed in δ ppm using TMS as an internal standard. Electron impact mass spectra were obtained at 70 eV using a GCMS-qp 1000 EX Shimadzu spectrometer (Japan). Reactions were routinely followed by thin layer chromatography (TLC) on silica gel F 254 aluminium sheets (Merck). The spots were detected by UV irradiation at 254–365 nm.

4-Aminobenzenesulfonamide **3a** was prepared by the reported method[9] mp 161–162°C.

N^1-Substituted 4-aminobenzenesulfonamides 3b–i : General Procedure

To a solution of appropriate amines, namely n-propylamine, benzyl amine, phenylhydrazine, aniline, p-toluidine, p-anisidine, 4-chloroaniline, and 4-nitroaniline (10 mmol) in dry pyridine (10 mL), crude p-acetamidobenzenesulfonyl chloride (2.34 g, 10 mmol) was added. The reaction mixture was heated at 70°C for 15 min, and set aside overnight at room temperature. The separated solid was filtered off, washed several times with water, and dried. The material was sufficiently pure for use in the following stage.

A mixture of acetamido derivative and sodium hydroxide (10 mL, 2 N) was gently heated under reflux for 1 h. The solution, when cooled to room temperature, neutralized with 50% dilute acetic acid until pH = 6.5. The solid product produced was filtered off with suction, dried, and recrystallized from ethanol (Table I).

General Procedure for the Preparation of 3-Substituted Amino-pyridazines 4a–i

A mixture of 3-chloro-5,6-diphenylpyridazine-4-carbonitrile **1** (1.0 mmol) and 4-aminobenzenesulfonamide derivatives **3a–i** (1.0 mmol) was refluxed in 1-butanol (20 mL) for 3 h. The reaction mixture was cooled to room temperature, and the separated solid

was filtered off, washed with water, dried, and recrystallized from ethanol (Tables II and III).

4-Cyano-5,6-diphenylpyridazine-3-sulfonylchloride 6

In a solution of 3-mercapto derivative **5** (1.0 g, 3.45 mmol) in acetic acid (9 mL) and water (1 mL), chlorine gas was bubbled at 0°C. After 2 h, the precipitate was filtered, washed with water several times, and dried to give 3-sulfonylchloride **6**, 1.10 g (95%). The respective crude sulfonylchloride, was used in the next step without further purification.

General Procedure for the Preparation of N-Substituted 4-Cyano-5,6-diphenylpyridazine-3-sulfonsmides 7a–k

To a solution of 4-cyano-5,6-diphenylpyridazine-3-sulfonylchloride **6** (1.0 g, 2.8 mmol) in benzene (20 mL), substituted amines (2.8 mmol) was added. The reaction mixture was heated under reflux for 3 h, then the solvent was concentrated. The solid product was collected, dried, and recrystallized from ethanol (Tables IV and V).

REFERENCES

[1] A. Deeb, El. S. Mourad, and D. Elenany, Part 27, *Z.Naturforsch.* (in press).
[2] M. Tisler and B. Stanovnik, In *Comperhensive Heterocyclic Chemistry*, ed. by A. R. Katritzky and C. W. Rees (Pergamon Press, Oxford, 1984), Vol. 3, pp. 1–56.
[3] A. Kleemann and J. Engel, *Pharmazeutische Wirkstoffe: Synthen, Patente, Anwendungen* (Thieme Verlag, Stuttgart, 1982).
[4] D. Lednicer, L. A. Mitscher, *The Organic Chemistry of Drug Synthesis* (Wiley, New York, 1984), Vol. 1, pp. 120, 1977; Vol. 2, pp. 112, 1980; Vol. 3, pp. 61.
[5] M. Hosny, F. El-Mariah, and A. Deeb, *Phosphorus, Sulfur, and Silicon*, **182,** 1475–1482, 2007.
[6] *Org. Syntheses* (Wiley, New York, 1976), Coll. Vol. III, p. 357.
[7] P. Schmidt and J. Druey, *Helv. Chim. Acta.*, **37,** 134 (1954).
[8] A. Deeb, S. A. Said, M. M. Hamed, and F. Yasin, *J. Chin. Chem. Soc.*, **37,** 287 (1991).
[9] *Vogel's Textbook of Practical Organic Chemistry* (Longman Group Limited, London, 1980), 4th ed., pp. 651.
[10] M. F. Ismail, N. A. Shams, and O. M. El-Sawy, *Synthesis,* 410 (1980).
[11] (a) R. O. Roblin and J. W. Clapp, *J. Am. Chem. Soc.*, **72**, 4890 (1950); (b) A. Deeb, A. Essawy, A. M. El-Gendy, and A. Shaban, *Monatshefte fur Chemie*, **121,** 281 (1990).
[12] P. J. Spendley and J. P. Ride, *Mycol. Soc.,* **82,** 283 (1984).