

Novel Regioselective Preparation of 5-Chloropyrazine-2-Carbonitrile from Pyrazine-2-Carboxamide and Coupling Study of Substituted Phenylsulfanylpurazine-2-Carboxylic Acid Derivatives

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Abstract: A new method of 5-chloropyrazine-2-carbonitrile preparation in a regioselective fashion and the study of the coupling of the pyrazine ring with variously substituted benzenethiols are described. A radical-ionic mechanism of this coupling, carried out in the presence of a heterogeneous copper catalyst, has been proposed. The reactivity of the substituted chloropyrazines is correlated to the calculated values of electronic deficiency in positions C₍₆₎ or C₍₅₎ of the pyrazine ring. This nucleophilic substitution provided a series of substituted phenylsulfanylpurazine-2-carboxylic acid derivatives. The synthetic approach, analytical and spectroscopic data of all compounds are presented.

1. INTRODUCTION

Halogenpyrazines are very important compounds in pyrazine chemistry, because of being important starting materials for further synthesis using nucleophilic substitution. Halogenpyrazine derivatives can be prepared in a number of different ways [1]. Halogenpyrazines are most frequently obtained *via* nucleophilic halogenation of pyrazine *N*-oxides [2-6] effected with phosphoryl chloride. The halogenation reaction mechanism of nonsubstituted pyrazine-*N*-oxide has been proposed [7].

Mono- or 1,4-dioxides are produced depending on the amount of hydrogen peroxide, temperature and reaction time [8-13], but a mixture of all products is obtained in all cases. That is, when the pyrazine nucleus is substituted, 3-carbamoylpyrazine-1-oxide and 2-carbamoylpyrazine-1-oxide and 2-carbamoylpyrazine-1,4-dioxide are formed simultaneously [14,15]. *N*-oxidation regioselectivity depends on substituent character [16], nevertheless 3-substituted pyrazine-1-oxide is the most frequently obtained product [16].

Chlorination regioselectivity depends on the character of the substituents and the substituent position in relation to the *N*-oxide group. When the mixture of *N*-oxides of pyrazine-2-carboxamide obtained in a classical way [8] was chlorinated by means of phosphoryl chloride, 6-chloropyrazine-2-carbonitrile (**3**) was obtained as the major product. 3-Chloropyrazine-2-carbonitrile (**5**) was obtained as a by-product and 5-chloropyrazine-2-carbonitrile (**4**) was generated in a minus amount. Sato has completed investigations in this area and proposed the reaction mechanism [17] the above dehydration/halogenation sequence.

5-Chloropyrazine-2-carbonitrile (**4**) is a key-compound in the synthesis of different structures with interesting antituberculosic and antifungal activity [18,19]. Thus, our work aimed at preparing 5-chloropyrazine-2-carbonitrile (**4**) in higher yields and then at preparing a series of substituted arylsulfanylpurazine-2-carboxylic acid derivatives from the above chloropyrazine-2-carbonitrile regioisomers, as some of the previously prepared alkyl- or arylsulfanylpurazine-2-carboxylic acid derivatives have shown antifungal activity [20].

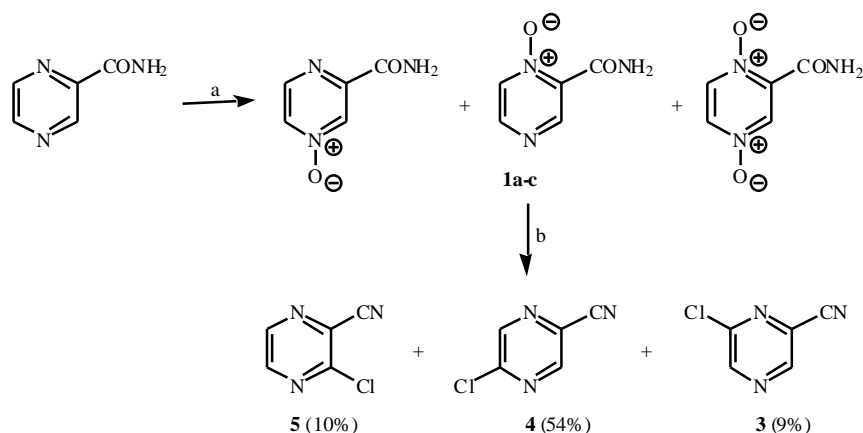
This is a follow-up paper to our previous article [21,22], where the study of the nucleophilic coupling of 4-methoxybenzene-1-thiol with 4-substituted aryl bromides was reported.

2. EXPERIMENTAL

2.1 Instrumentation and Chemicals

All solvents used for the synthesis were of analytical grade. The solvents were dried and freshly distilled under an argon atmosphere. Copper catalyst Cu₂O (powder, 97% purity) was purchased from Sigma-Aldrich. Kieselgel 60, 0.040-0.063 mm (Merck, Germany) was used for flash chromatography (*F_c*). TLC was performed on Silufol UV 254 plates (Kavalier, Votice, Czech Republic) in the following solvent systems: EtOAc/petroleum ether (3:7) (A); EtOAc/petroleum ether (3:2) (B); EtOAc/petroleum ether (1:4) (C); EtOAc/petroleum ether (1:1) (D). The plates were illuminated under UV (254 nm) and the spots were visualised using the solution of Bromothymol Blue in NaOH. The melting points were determined on Boetius PHMK 05 (VEB Kombinat Nagema, Radebeul, Germany) and are uncorrected. Elemental analyses were carried out on an automatic microanalyser EA1110CE (CE Instruments, Milano, Italy). Infrared spectra were recorded with neat oils (for non-crystalline materials) and in KBr pellets (for crystalline materials) on an IR-spectrometer Nicolet Impact

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Reagents: a) 2 mol 30% H₂O₂, 99% AcOH, 6 h reflux; b) POCl₃.

Scheme 1. The modified preparation of *N*-oxide mixture of pyrazine-2-carboxamides (**1a-c**) and the following dehydration/halogenation provided a carbonitrile mixture **3-5** in 73% yield.

400. ¹H and ¹³C NMR Spectra were recorded on a Varian Mercury – Vx BB 300 (299.95 MHz for ¹H and 75.43 MHz for ¹³C), Bruker Comp. (Karlsruhe, Germany). Chemical shifts are given relative to internal Si(CH₃)₄.

The comparative HPLC system, consisting of a binary pump LCP 4100 (Ecom, Prague), Waters autosampler 717 plus, variable wavelength UV detector Waters 486 (Waters, Milford, MA) and a PC for data processing, was controlled by chromatographic software CSW v.1.7 for Windows (Data Apex s.r.o., Prague). A mobile phase was the mixture of MeCN – water (10 : 90), a flow rate of the column was 5 ml/min, a column Zorbax TMS, 5 μm, 4.6×250 mm, HPST, injection 5 μl of sample MeOH, UV detection by 210 nm.

2.2 Synthesis

Mixture of *N*-oxides of Pyrazine-2-carboxamides (1a-c). Modified preparation, see Scheme 1 for conditions. A pure white crystalline product was obtained by means of crystallisation from water. Yield: 46%. M.p. 278-284 °C.

Mixture of *N*-oxides of Pyrazine-2-carboxamides (2a-c). Conditions [23], see Scheme 2. Yield: 49%. M.p. 308-310 °C; M.p. 302-305 °C [12,23,24].

Chloropyrazine-2-carbonitrile Mixture (3-5). Conditions [5]. *F_C* (EtOAc/petroleum ether 1:4) provided colourless crystalline individual isomers. General yield was 73% from **1**, 76% from **2**.

6-Chloropyrazine-2-carbonitrile (3). Colourless crystalline compound. Yield: 57% (mixture **1**), 9% (mixture **2**). *R_F*: 0.79 (A). M.p. 24-26 °C; colourless viscous oil [5].

5-Chloropyrazine-2-carbonitrile (4). Colourless crystalline compound. Yield: 2% (mixture **1**), 54% (mixture **2**). *R_F*: 0.56 (A). M.p. 44-45 °C; M.p. 46-47 °C [6].

3-Chloropyrazine-2-carbonitrile (5). Colourless crystalline compound. Yield: 17% (mixture **1**), 10% (mixture **2**). *R_F*: 0.40 (A). M.p. 48 °C; M.p. 48 °C [5].

6-Chloropyrazine-2-carboxylic acid (6). The hydrolysis of nitrile **3**. Conditions [25,29]. A white crystalline compound. Yield: 96%. *R_F*: 0.55 (B). M.p. 158-160 °C; M.p. 160-161 °C [26].

3-Chloropyrazine-2-carboxylic acid (7). The hydrolysis of nitrile **5**. Conditions [25]. A white crystalline compound. Yield: 90%. *R_F*: 0.10 (B). M.p. 119-121 °C; M.p. 117-118 °C [26].

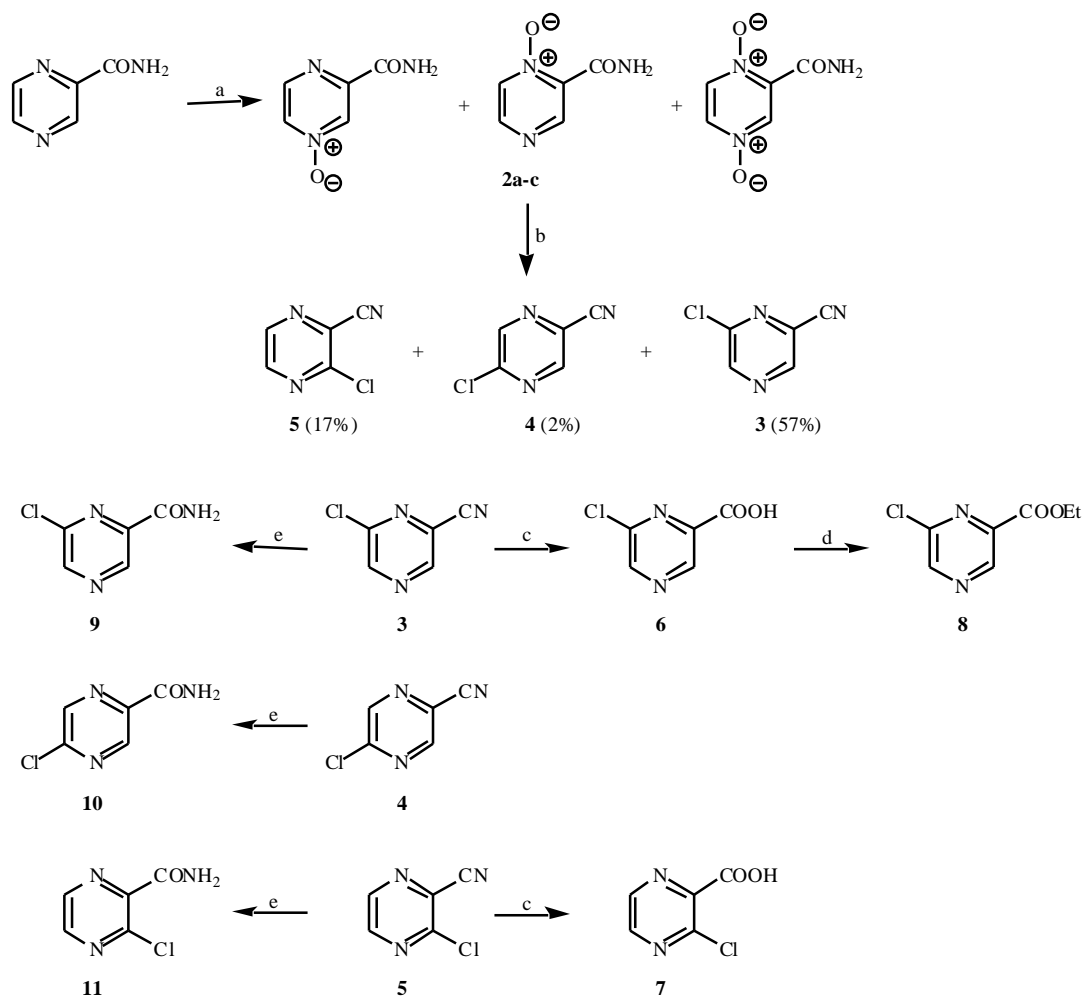
Ethyl 6-chloropyrazine-2-carboxylate (8). Esterification of acid **6**. Conditions [4]. *F_C* (EtOAc/petroleum ether 1:8) provided colourless oil. Yield: 99%. *R_F*: 0.84 (B). Anal. Calc. for C₇H₇ClN₂O₂ (186.60): 45.06% C, 3.78% H, 15.01% N; found: 45.10% C, 3.81% H, 14.98% N. IR spectrum (neat), cm⁻¹: 1732 (ester), 1437, 1247, 1180 (pyrazine). ¹H NMR (300 MHz, CDCl₃), δ: 9.18 (d, 1H, *J*=0.62 Hz, H3), 8.76 (d, 1H, *J*=0.63 Hz, H5), 4.50 (q, 2H, *J*=7.14 Hz, OCH₂), 1.44 (t, 3H, *J*=7.14 Hz, CH₃). ¹³C NMR (75 MHz, CDCl₃), δ: 162.7, 149.2, 147.9, 143.6, 142.8, 62.7, and 14.2.

6-Chloropyrazine-2-carboxamide (9). Partial hydrolysis of nitrile **3**. Conditions [25]. A white crystalline compound. Yield: 62%. *R_F*: 0.32 (A). M.p. 180-182 °C; M.p. 176-177 °C [5].

5-Chloropyrazine-2-carboxamide (10). Partial hydrolysis of nitrile **4**. Conditions [25]. A white crystalline compound. Yield: 58%. *R_F*: 0.43 (A). M.p. 170-172 °C; M.p. 171-172 °C [5].

3-Chloropyrazine-2-carboxamide (11). Partial hydrolysis of nitrile **5**. Conditions [25]. A white crystalline compound. Yield: 63%. *R_F*: 0.21 (A). M.p. 192-194 °C; M.p. 186-187 °C [27].

6-[(4-Methoxyphenyl)sulfanyl]pyrazine-2-carbonitrile (12). Method A: Thiol (5.0 mmol) was added slowly to an ice-cool dry EtOH (50 ml) with EtONa (Na 5.5 mmol, in case of acids coupling 8.5 mmol). A substituted chloropyrazine-2-carboxylic acid derivative (3.3 mmol) was then added, and the mixture was refluxed under argon for 3 h. Then the solvent was removed at reduced pressure, the solid residue suspended in water (in case of acids coupling, water was acidified) and extracted with EtOAc. The combined organic extracts were dried over anhydrous MgSO₄ and filtered. The solvent was removed at reduced pressure.



Reagents: a) 2 mol 30% H_2O_2 , 99% AcOH, 8 h, 70 °C; b) POCl_3 ; c) *i*, NaOH, *ii* HCl; d) toluene, SOCl_2 , EtOH, TEA; e) 35% H_2O_2 , H_2O , NaOH.

Scheme 2. Standard preparation of *N*-oxide mixture of pyrazine-2-carboxamides (**2a-c**) [23] and preparation of intermediates **6-11** for further syntheses. Preparation of **2** and the following dehydration/halogenation provided a carbonitrile mixture **3-4** in 76% yield.

Method B: Thiol (5.0 mmol) was added slowly to an ice-cool suspension of NaH (60% dispersion in mineral oil, 6.0 mmol, in case of acids coupling 10.2 mmol) in dry DMF (15 ml). The mixture was stirred for a few minutes until the evolution of hydrogen gas stopped. A substituted chloropyrazine-2-carboxylic acid derivative (3.3 mmol) was then added, and the mixture was refluxed under argon for 1 h. The cooled mixture was poured onto ice and extracted with EtOAc. The combined organic extracts were washed with aqueous ammonia (35%) (except acids coupling) and water, dried over anhydrous MgSO_4 and filtered. The solvent was removed at reduced pressure.

Method C: The same as Method B. Copper(I) oxide (0.8 mmol) was used in this case.

F_C (EtOAc/petroleum ether 1:9) gave a light yellow oil. Yields, see Table 1. R_F : 0.60 (D). Anal. Calc. for $\text{C}_{12}\text{H}_9\text{N}_3\text{OS}$ (243.29): 59.24% C, 3.73% H, 17.27% N, 13.18% S; found: 59.29% C, 3.69% H, 17.20% N, 13.10% S. IR spectrum (neat), cm^{-1} : 2242 (CN), 1593 (Ph), 1463 (OCH_3), 1370, 1289, 1170 (pyrazine), 1111 (S-Ph). ^1H NMR (300 MHz, CDCl_3): 8.76 (d, 1H, $J=0.60$ Hz, H3), 8.65 (d, 1H, $J=0.61$

Hz, H5), 7.52-7.45 (m AA'BB', 2H, H2', H6'), 7.09-7.03 (m AA'BB', 2H, H3', H5'), 3.81 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, CDCl_3): 162.0, 161.6, 148.1, 146.0, 137.7, 128.8, 116.5, 115.6, 115.2, and 55.6.

6-[(3-Methoxyphenyl)sulfanyl]pyrazine-2-carbonitrile (13). The coupling of nitrile **3**. Conditions, see compound **12**. Yields, see Table 1. F_C (EtOAc/petroleum ether 1:9) gave a light yellow oil. R_F : 0.53 (A). Anal. Calc. for $\text{C}_{12}\text{H}_9\text{N}_3\text{OS}$ (243.29): 59.24% C, 3.73% H, 17.27% N, 13.18% S; found: 59.25% C, 3.77% H, 17.24% N, 13.11% S. IR spectrum (neat), cm^{-1} : 2242 (CN), 1593 (Ph), 1469 (OCH_3), 1373, 1289, 1149 (pyrazine), 1110 (S-Ph). ^1H NMR (300 MHz, CDCl_3): 8.79 (d, 1H, $J=0.63$ Hz, H3), 8.65 (d, 1H, $J=0.63$ Hz, H5), 7.39 (t, 1H, $J=7.96$ Hz, H5'), 7.17 (m, 1H, H6'), 7.14-7.11 (m, 1H, H2'), 7.06-7.00 (m, 1H, H4'), and 3.78 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, CDCl_3): 162.1, 160.6, 148.4, 146.2, 130.6, 129.6, 128.9, 120.7, 115.9, 114.3, 113.1, and 55.6.

6-(Phenylsulfanyl)pyrazine-2-carbonitrile (14). The coupling of nitrile **3**. Conditions, see compound **12**. Yields, see Table 6. F_C (EtOAc/petroleum ether 1:9) gave a light

Table 1. Yields and conditions of the coupling and the charges calculated values of the electronic deficiencies in position C₆ of the pyrazine ring. (A: EtOH, Na, 3 h; B: DMF, NaH, 1 h; C: Cu₂O, DMF, NaH, 20 min).

Reactant	Product	Conditions	Yields [%]	Charges [0] ^a	Charges [+1] ^b
3	12	A	51	-0.16	0.40
		B	39	-0.17	0.34
		C	81	-0.17	0.34
6	15	A	38	-0.22	0.41
		B	30	-0.23	0.40
		C	73	-0.23	0.40
8	17	A	28	-0.17	0.44
		B	12	-0.16	0.36
		C	61	-0.16	0.36
9	18	A	22	-0.27	0.39
		B	8	-0.45	0.35
		C	49	-0.45	0.35
3	13	A	63	-0.16	0.40
		B	41	-0.17	0.34
		C	84	-0.17	0.34
6	16	A	46	-0.22	0.41
		B	44	-0.23	0.40
		C	79	-0.23	0.40
8	19	A	33	-0.27	0.39
		B	25	-0.45	0.35
		C	52	-0.45	0.35

^a atomic charges at a former position of the chlorine in reactant, formal charge of a molecule 0, ^b *ibid.*, formal charge +1.

yellow crystalline compound. R_f : 0.65 (D). M.p. 74-76 °C; M.p. 75-78 °C [25].

6-[(4-Methoxyphenyl)sulfanyl]pyrazine -2- carboxylic Acid (15).

Method A: The hydrolysis of nitrile **12**. Conditions [25]. Yield: 87%.

Method B: The hydrolysis of ester **17**. Conditions [25]. Yield: 92%.

Method C: The hydrolysis of amide **18**. Conditions [25]. Yield: 90%.

Metoda D: The coupling of acid **6**. Conditions, see compound **12**. Yields, see Table 1.

F_C (EtOAc/petroleum ether 1:4) gave a white crystalline compound. R_f : 0.16 (A). M.p. 154-156 °C. Anal. Calc. for C₁₂H₁₀N₂O₃S (262.29): 54.95% C, 3.84% H, 10.68% N, 12.22% S; found: 55.00% C, 3.89% H, 10.61% N, 12.19% S. IR spectrum (KBr), cm⁻¹: 3330 (acid), 1589 (Ph), 1466 (OCH₃), 1390, 1274, 1140 (pyrazine), 1110 (S-Ph). ¹H NMR (300 MHz, DMSO-*d*₆), : 8.83 (d, 1H, $J=0.52$ Hz, H3), 8.28 (d, 1H, $J=0.52$ Hz, H5), 7.64-7.57 (m AA'BB', 2H, H2', H6'), 7.12-7.05 (m AA'BB', 2H, H3', H5'), and 3.81 (s, 3H, OCH₃). ¹³C NMR (75 MHz, DMSO-*d*₆), : 164.8, 161.0, 158.7, 144.1, 143.0, 141.0, 137.2, 117.9, 116.1, and 55.6.

6-[(3-Methoxyphenyl)sulfanyl]pyrazine -2- carboxylic Acid (16).

Method A: The hydrolysis of nitrile **13**. Conditions [25]. Yield: 84%.

Method B: The hydrolysis of amide **19**. Conditions [25]. Yield: 89%.

Method C: The coupling of acid **6**. Conditions, see compound **12**. Yields, see Table 1.

F_C (EtOAc/petroleum ether 1:4) gave a light yellow crystalline compound. R_f : 0.21 (A). M.p. 124-126 °C. Anal. Calc. for C₁₂H₁₀N₂O₃S (262.29): 54.95% C, 3.84% H, 10.68% N, 12.22% S; found: 55.02% C, 3.87% H, 10.65% N, 12.20% S. IR spectrum (KBr), cm⁻¹: 3330 (acid), 1590 (Ph), 1460 (OCH₃), 1393, 1278, 1150 (pyrazine), 1111 (S-Ph). ¹H NMR (300 MHz, DMSO-*d*₆), : 8.88 (d, 1H, $J=0.50$ Hz, H3), 8.38 (d, 1H, $J=0.50$ Hz, H5), 7.42 (t, 1H, $J=7.96$ Hz, H5'), 7.26 (t, 1H, $J=2.19$ Hz, H6'), 7.24-7.18 (m, 1H, H2'), 7.11-7.04 (m, 1H, H4'), and 3.78 (s, 3H, OCH₃). ¹³C NMR (75 MHz, DMSO-*d*₆), : 164.8, 160.3, 157.1, 145.1, 143.2, 141.5, 131.1, 129.6, 126.3, 119.3, 116.1, and 55.6.

Ethyl 6-[(4-methoxyphenyl)sulfanyl]pyrazine-2-carboxylate (17). The coupling of ester **8**. Conditions, see compound **12**. Yields, see Table 1. F_C (EtOAc/petroleum ether 3:7) gave a white crystalline compound. R_f : 0.45 (C).

M.p. 68-70 °C. Anal. Calc. for C₁₄H₁₄N₂O₃S (290.34): 57.92% C, 4.86% H, 9.65% N, 11.04% S; found: 57.96% C, 4.90% H, 9.61% N, 10.98% S. IR spectrum (KBr), cm⁻¹: 1730 (ester), 1589 (Ph), 1470 (OCH₃), 1370, 1291, 1148 (pyrazine), 1112 (S-Ph). ¹H NMR (300 MHz, CDCl₃), : 8.88 (d, 1H, $J=0.60$ Hz, H3), 8.12 (d, 1H, $J=0.61$ Hz, H5), 7.60-7.54 (m AA'BB', 2H, H2', H6'), 7.04-6.96 (m AA'BB', 2H, H3', H5'), 4.47 (q, 2H, $J=7.14$ Hz, OCH₂), 3.86 (s, 3H, OCH₃), and 1.42 (t, 3H, $J=7.14$ Hz, CH₃). ¹³C NMR (75 MHz, CDCl₃), : 164.7, 160.9, 157.8, 144.1, 143.1, 140.9, 137.2, 118.0, 116.0, 63.2, 55.6, and 15.7.

6-[(4-Methoxyphenyl)sulfanyl]pyrazine -2- carboxamide (18). The coupling of amide **9**. Conditions, see

Table 2. Yields and conditions of the coupling and the charges calculated values of the electronic deficiencies in position C₅ of the pyrazine ring. (A: EtOH, Na, 3 h; B: DMF, NaH, 1 h; C: Cu₂O, DMF, NaH, 20 min).

Reactant	Product	Conditions	Yields [%]	Charges [0] ^a	Charges [+1] ^b
4	20	A	67	-0.12	0.45
		B	38	-0.13	0.37
		C	90	-0.13	0.37
10	22	A	41	-0.12	0.43
		B	10	-0.12	0.37
		C	62	-0.12	0.37
4	21	A	74	-0.12	0.45
		B	40	-0.13	0.37
		C	92	-0.13	0.37
10	23	A	53	-0.12	0.43
		B	25	-0.12	0.37
		C	66	-0.12	0.37

^a atomic charges at a former position of the chlorine in reactant, formal charge of a molecule 0, ^b *ibid.*, formal charge +1.

compound **12**. Yields, see Table 1. F_C (EtOAc/petroleum ether 1:9) gave a white crystalline compound. R_F : 0.39 (D). M.p. 136-138 °C. Anal. Calc. for C₁₂H₁₁N₃O₂S (261.30): 55.16% C, 4.24% H, 16.08% N, 12.27% S; found: 55.22% C, 4.20% H, 16.05% N, 12.23% S. IR spectrum (KBr), cm⁻¹: 3422 (amide), 1592 (Ph), 1470 (OCH₃), 1370, 1292, 1145 (pyrazine), 1110 (S-Ph). ¹H NMR (300 MHz, CDCl₃), : 8.78 (d, 1H, $J=0.60$ Hz, H3), 8.33 (bs, 1H, NH₂), 8.22 (d, 1H, $J=0.60$ Hz, H5), 7.97 (bs, 1H, NH₂), 7.60-7.55 (m AA'BB', 2H, H2', H6'), 7.12-7.05 (m AA'BB', 2H, H3', H5'), and 3.81 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 165.9, 163.9, 161.8, 144.1, 143.1, 141.0, 137.2, 117.9, 115.2, and 55.6.

6-[(3-Methoxyphenyl)sulfanyl]pyrazin -2- carboxamide (19). The coupling of amide **9**. Conditions, see compound **12**. Yields, see Table 1. F_C (EtOAc/petroleum ether 1:9) gave a light yellow crystalline compound. R_F : 0.25 (A). M.p. 116-118 °C. Anal. Calc. for C₁₂H₁₁N₃O₂S (261.30): 55.16% C, 4.24% H, 16.08% N, 12.27% S; found: 55.20% C, 4.27% H, 16.02% N, 12.19% S. IR spectrum (KBr), cm⁻¹: 3422 (amide), 1591 (Ph), 1465 (OCH₃), 1375, 1290, 1150 (pyrazine), 1110 (S-Ph). ¹H NMR (300 MHz, CDCl₃), : 8.84 (d, 1H, $J=0.65$ Hz, H3), 8.34 (bs, 1H, NH₂), 8.25 (d, 1H, $J=0.65$ Hz, H5), 7.97 (bs, 1H, NH₂), 7.38 (t, 1H, $J=7.94$ Hz, H5'), 7.24 (m, 1H, H6'), 7.20-7.16 (m, 1H, H2'), 7.08-7.01 (m, 1H, H4'), and 3.73 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 166.0, 164.0, 160.9, 145.1, 143.0, 141.5, 130.5, 129.6, 126.5, 121.0, 115.7, and 55.6.

5-[(4-Methoxyphenyl)sulfanyl]pyrazine-2-carbonitrile (20). The coupling of nitrile **4**. Conditions, see compound **12**. Yields, see Table 2. F_C (EtOAc/petroleum ether 1:9) gave a light yellow crystalline compound. R_F : 0.62 (D). M.p. 51-53 °C. Anal. Calc. for C₁₂H₉N₃OS (243.29): 59.24% C, 3.73% H, 17.27% N, 13.18% S; found: 59.27% C, 3.70% H, 12.23% N, 13.13% S. IR spectrum (KBr), cm⁻¹: 2260 (CN), 1594 (Ph), 1459 (OCH₃), 1397, 1252, 1171 (pyrazine), 1109 (S-Ph). ¹H NMR (300 MHz, CDCl₃), : 8.86 (d, 1H, $J=1.41$ Hz, H3), 8.80 (d, 1H, $J=1.41$ Hz, H6), 7.55-7.50 (m AA'BB', 2H, H2', H6'), 7.04-6.98 (m AA'BB', 2H, H3', H5'), and 3.80 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 161.7, 161.5, 144.5, 142.7, 137.3, 129.3, 116.8, 115.8, 115.2, and 55.5.

5-[(3-Methoxyphenyl)sulfanyl]pyrazine-2-carbonitrile (21). The coupling of nitrile **4**. Conditions, see compound **12**. Yields, see Table 2. F_C (EtOAc/petroleum ether 1:9) gave a light yellow oil. R_F : 0.58 (A). Anal. Calc. for C₁₂H₉N₃OS (243.29): 59.24% C, 3.73% H, 17.27% N, 13.18% S; found: 59.30% C, 3.77% H, 17.21% N, 13.11% S. IR spectrum (neat), cm⁻¹: 2213 (CN), 1595 (Ph), 1467 (OCH₃), 1365, 1290, 1150 (pyrazine), 1108 (S-Ph). ¹H NMR (300 MHz, CDCl₃), : 8.87 (d, 1H, $J=1.40$ Hz, H3), 8.83 (d, 1H, $J=1.41$ Hz, H6), 7.40 (t, 1H, $J=7.93$ Hz, H5'), 7.29 (m, 1H, H6'), 7.20-7.14 (m, 1H, H2'), 7.05-7.00 (m, 1H, H4'), and 3.78 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 161.3, 160.3, 144.7, 142.6, 131.4, 129.7, 129.1, 121.0, 116.7, 114.3, 113.2, and 55.4.

5-[(4-Methoxyphenyl)sulfanyl]pyrazine -2- carboxamide (22). The coupling of amide **10**. Conditions, see compound **12**. Yields, see Table 2. F_C (EtOAc/petroleum ether 1:9) gave a light yellow crystalline compound. R_F : 0.44 (D). M.p. 122-124 °C. Anal. Calc. for C₁₂H₁₁N₃O₂S (261.30): 55.16% C, 4.24% H, 16.08% N, 12.27% S; found: 55.21% C, 4.32% H, 15.96% N, 12.19% S. IR spectrum (KBr), cm⁻¹: 3425 (amide), 1591 (Ph), 1465 (OCH₃), 1367, 1271, 1150 (pyrazine), 1109 (S-Ph). ¹H NMR (300 MHz, CDCl₃), : 9.06 (d, 1H, $J=1.40$ Hz, H3), 8.82 (d, 1H, $J=1.41$ Hz, H6), 8.38 (bs, 1H, NH₂), 7.95 (bs, 1H, NH₂), 7.57-7.52 (m AA'BB', 2H, H2', H6'), 7.06-6.98 (m AA'BB', 2H, H3', H5'), and 3.80 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 165.2, 160.7, 158.8, 144.8, 144.1, 143.6, 137.3, 118.0, 115.1, and 55.5.

5-[(3-Methoxyphenyl)sulfanyl]pyrazine -2- carboxamide (23). The coupling of amide **10**. Conditions, see compound **12**. Yields, see Table 2. F_C (EtOAc/petroleum ether 1:9) gave a light yellow crystalline compound. R_F : 0.43 (A). M.p. 97-99 °C. Anal. Calc. for C₁₂H₁₁N₃O₂S (261.30): 55.16% C, 4.24% H, 16.08% N, 12.27% S; found: 55.23% C, 4.29% H, 16.02% N, 12.22% S. IR spectrum (KBr), cm⁻¹: 3425 (amide), 1589 (Ph), 1467 (OCH₃), 1368, 1273, 1148 (pyrazine), 1110 (S-Ph). ¹H NMR (300 MHz, CDCl₃), : 9.04 (d, 1H, $J=1.40$ Hz, H3), 8.88 (d, 1H, $J=1.41$ Hz, H6), 8.37 (bs, 1H, NH₂), 7.95 (bs, 1H, NH₂), 7.41 (t, 1H, $J=7.90$ Hz, H5'), 7.24 (m, 1H, H6'), 7.20-7.15 (m, 1H, H2'), 7.05-7.00 (m, 1H, H4'), and 3.78 (s, 3H, OCH₃). ¹³C NMR (75

Table 3. Yields and conditions of the coupling and the charges calculated values of the electronic deficiencies in position C₃ of the pyrazine ring. (A: EtOH, Na, 3 h; B: DMF, NaH, 1 h; C: Cu₂O, DMF, NaH, 20 min).

Reactant	Product	Conditions	Yields [%]	Charges [0] ^a	Charges [+1] ^b
5	24	A	53	-0.15	0.37
		B	39	-0.17	0.31
		C	83	-0.17	0.31
7	26	A	38	-0.12	0.27
		B	32	-0.16	0.22
		C	74	-0.16	0.22
11	28	A	38	-0.16	0.66
		B	10	-0.18	0.25
		C	57	-0.18	0.25
5	25	A	65	-0.15	0.37
		B	41	-0.17	0.31
		C	85	-0.17	0.31
7	27	A	48	-0.12	0.27
		B	45	-0.16	0.22
		C	80	-0.16	0.22
11	29	A	42	-0.16	0.66
		B	25	-0.18	0.25
		C	59	-0.18	0.25

^a atomic charges at a former position of the chlorine in reactant, formal charge of a molecule 0, ^b *ibid.*, formal charge +1.

MHz, CDCl₃), : 165.0, 160.5, 157.5, 145.0, 144.6, 143.9, 130.8, 128.8, 127.4, 120.3, 116.1, and 55.5.

3-[(4-Methoxyphenyl)sulfanyl]pyrazine-2-carbonitrile (24). The coupling of nitrile **5**. Conditions, see compound **12**. Yields, see Table 3. *F_C* (EtOAc/petroleum ether 1:9) gave a light yellow crystalline compound. *R_F*: 0.58 (D). M.p. 111-113 °C. Anal. Calc. for C₁₂H₉N₃OS (243.29): 59.24% C, 3.73% H, 17.27% N, 13.18% S; found: 59.28% C, 3.68% H, 17.20% N, 13.11% S. IR spectrum (KBr), cm⁻¹: 2241 (CN), 1593 (Ph), 1463 (OCH₃), 1372, 1292, 1165 (pyrazine), 1111 (S-Ph). ¹H NMR (300 MHz, CDCl₃), : 8.69 (d, 1H, *J*=2.34 Hz, H₆), 8.59 (d, 1H, *J*=2.34 Hz, H₅), 7.55-7.48 (m AA'BB', 2H, H₂', H₆'), 7.08-7.02 (m AA'BB', 2H, H₃', H₅'), and 3.80 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 161.1, 160.6, 147.0, 143.7, 137.5, 130.3, 116.5, 115.6, 115.1, and 55.6.

3-[(3-Methoxyphenyl)sulfanyl]pyrazine-2-carbonitrile (25). The coupling of nitrile **5**. Conditions, see compound **12**. Yields, see Table 3. *F_C* (EtOAc/petroleum ether 1:9) gave a light yellow crystalline compound. *R_F*: 0.46 (A). M.p. 82-85 °C. Anal. Calc. for C₁₂H₉N₃OS (243.29): 59.24% C, 3.73% H, 17.27% N, 13.18% S; found: 59.29% C, 3.76% H, 17.23% N, 13.09% S. IR spectrum (KBr), cm⁻¹: 2243 (CN), 1593 (Ph), 1469 (OCH₃), 1370, 1289, 1149 (pyrazine), 1112 (S-Ph). ¹H NMR (300 MHz, CDCl₃), : 8.67 (d, 1H, *J*=2.33 Hz, H₆), 8.59 (d, 1H, *J*=2.33 Hz, H₅), 7.38 (t, 1H, *J*=7.96 Hz, H₅'), 7.19 (m, 1H, H₆'), 7.13-7.10 (m, 1H, H₂'), 7.06-7.00 (m, 1H, H₄'), and 3.78 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 161.3, 160.2, 146.8, 143.5, 130.8, 130.7, 129.7, 120.7, 116.2, 114.3, 113.1, and 55.4.

3-[(4-Methoxyphenyl)sulfanyl]pyrazine-2-carboxylic Acid (26).

Method A: The hydrolysis of nitrile **24**. Conditions [25]. Yield: 80%.

Method B: The hydrolysis of amide **28**. Conditions [25]. Yield: 83%.

Method C: The coupling of acid **7**. Yields, see Table 3.

The crude compound was purified by acetone. A pure white insoluble crystalline compound was obtained. M.p. 114-116 °C. Anal. Calc. for C₁₂H₁₀N₂O₃S (262.29): 54.95% C, 3.84% H, 10.68% N, 12.22% S; found: 55.00% C, 3.84% H, 10.66% N, 12.20% S. IR spectrum (KBr), cm⁻¹: 3332 (acid), 1590 (Ph), 1460 (OCH₃), 1395, 1281, 1152 (pyrazine), 1110 (S-Ph).

6-[(3-Methoxyphenyl)sulfanyl]pyrazine-2-carboxylic Acid (27).

Method A: The hydrolysis of nitrile **25**. Conditions [25]. Yield: 78%.

Method B: The hydrolysis of amide **29**. Conditions [25]. Yield: 82%.

Method C: The coupling of acid **7**. Yields, see Table 3.

The crude compound was purified by acetone. A pure light yellow insoluble crystalline compound was obtained. M.p. 90-92 °C. Anal. Calc. for C₁₂H₁₀N₂O₃S (262.29): 54.95% C, 3.84% H, 10.68% N, 12.22% S; found: 55.03% C, 3.88% H, 10.63% N, 12.19% S. IR spectrum (KBr), cm⁻¹: 3330 (acid), 1589 (Ph), 1463 (OCH₃), 1390, 1280, 1151 (pyrazine), 1111 (S-Ph).

3-[(4-Methoxyphenyl)sulfanyl]pyrazine-2-carboxamide (28). The coupling of amide **11**. Yields, see Table 3. *F_C* (EtOAc/petroleum ether 1:9) gave a white crystalline compound. *R_F*: 0.36 (D). M.p. 191-193 °C. Anal. Calc. for C₁₂H₁₁N₃O₂S (261.30): 55.16% C, 4.24% H, 16.08% N, 12.27% S; found: 55.21% C, 4.23% H, 16.04% N, 12.23% S. IR spectrum (KBr), cm⁻¹: 3420 (amide), 1593 (Ph), 1470 (OCH₃), 1373, 1289, 1149 (pyrazine), 1110 (S-Ph). ¹H NMR (300 MHz, CDCl₃), : 8.73 (d, 1H, *J*=2.35 Hz, H₆), 8.67 (d, 1H, *J*=2.35 Hz, H₅), 8.31 (bs, 1H, NH₂), 8.06 (bs, 1H, NH₂),

7.62-7.57 (m AA'BB', 2H, H2', H6'), 7.10-7.04 (m AA'BB', 2H, H3', H5'), and 3.81 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 165.9, 162.0, 158.8, 146.2, 145.8, 143.8, 137.9, 118.1, 115.9, and 55.6.

3-[(3-Methoxyphenyl)sulfanyl]pyrazine-2-carboxamide (29). The coupling of amide **11**. Yields, see Table 3. *F_C* (EtOAc/petroleum ether 1:9) gave a light yellow crystalline compound. *R_F*: 0.21 (A). M.p. 162-164 °C. Anal. Calc. for C₁₂H₁₁N₃O₂S (261.30): 55.16% C, 4.24% H, 16.08% N, 12.27% S; found: 55.19% C, 4.26% H, 16.00% N, 12.19% S. IR spectrum (KBr), cm⁻¹: 3420 (amide), 1591 (Ph), 1465 (OCH₃), 1373, 1290, 1154 (pyrazine), 1110 (S-Ph). ¹H NMR (300 MHz, CDCl₃), : 8.71 (d, 1H, *J*=2.35 Hz, H6), 8.68 (d, 1H, *J*=2.35 Hz, H5), 8.29 (bs, 1H, NH₂), 7.99 (bs, 1H, NH₂), 7.34 (t, 1H, *J*=7.94 Hz, H5'), 7.23 (m, 1H, H6'), 7.16-7.12 (m, 1H, H2'), 7.03-7.68 (m, 1H, H4'), and 3.78 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 166.5, 159.8, 159.3, 146.1, 145.5, 143.9, 130.8, 129.7, 128.1, 121.0, 115.3, and 55.3.

Methyl 6-methoxypyrazine-2-carboxylate (30). The esterification and substitution of acid **6** by means of methyl chlorosulfinate. Conditions [28]. *F_C* (EtOAc/petroleum ether 7:2) provided a white crystalline compound. Yield: 86%. *R_F*: 0.65 (B). M.p. 81.5-82 °C; M.p. 82 °C [29].

Bis(4-methoxyphenyl)disulfide (31). Generated by the coupling (see compound **12**) of 4-methoxybenzene-1-thiol as a by-product. Yields were condition-dependent 26-30%. A light yellow crystalline compound. *R_F*: 0.52 (B). M.p. 39-39.5 °C [30].

4-Methoxyphenyl 6-chloropyrazine-2-carbothioimide (32). Generated along with nitrile **12**, method B as a by-product. Yield: 40%. *F_C* (EtOAc/petroleum ether 1:9) gave a light yellow oil. *R_F*: 0.47 (D). Anal. Calc. for C₁₂H₁₀ClN₃OS (279.75): 51.52% C, 3.60% H, 15.02% N, 11.46% S; found: 51.58% C, 3.64% H, 14.98% N, 11.39% S. IR spectrum (neat), cm⁻¹: 3432 (NH), 1710 (thioester), 1592 (Ph), 1490 (C=N), 1463 (OCH₃), 1405, 1258, 1180 (pyrazine). ¹H NMR (300 MHz, CDCl₃), : 9.89 (bs, 1H, NH), 8.79 (d, 1H, *J*=0.60 Hz, H3), 8.25 (d, 1H, *J*=0.60 Hz, H5), 7.60-7.54 (m AA'BB', 2H, H2', H6'), 7.10-7.05 (m AA'BB', 2H, H3', H5'), and 3.81 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 162.1, 161.5, 144.1, 143.9, 143.1, 141.1, 137.7, 117.2, 115.6, and 55.6.

3-Methoxyphenyl 6-chloropyrazine-2-carbothioimide (33). Generated along with nitrile **13**, method B as a by-product. Yield: 34%. *F_C* (EtOAc/petroleum ether 1:9) gave a light yellow oil. *R_F*: 0.40 (A). Anal. Calc. for C₁₂H₁₀ClN₃OS (279.75): 51.52% C, 3.60% H, 15.02% N, 11.46% S; found: 51.55% C, 3.69% H, 14.96% N, 11.40% S. IR spectrum (neat), cm⁻¹: 3433 (NH), 1716 (thioester), 1593 (Ph), 1492 (C=N), 1462 (OCH₃), 1405, 1253, 1181 (pyrazine). ¹H NMR (300 MHz, CDCl₃), : 9.83 (bs, 1H, NH), 8.83 (d, 1H, *J*=0.63 Hz, H3), 8.24 (d, 1H, *J*=0.63 Hz, H5), 7.38 (t, 1H, *J*=7.93 Hz, H5'), 7.20 (m, 1H, H6'), 7.19-7.14 (m, 1H, H2'), 6.99-6.92 (m, 1H, H4'), and 3.78 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 162.0, 161.5, 146.0, 145.8, 144.2, 142.0, 130.5, 129.7, 126.5, 119.7, 115.4, and 55.5.

Phenyl 6-chloropyrazine-2-carbothioimide (34). Generated along with nitrile **14**, method B as a by-product. Yield: 38%. *F_C* (EtOAc/petroleum ether 1:9) gave a light yellow oil. *R_F* (D) 0.54. Anal. Calc. for C₁₁H₈ClN₃S

(249.72): 52.91% C, 3.23% H, 16.83% N, 12.84% S; found: 52.97% C, 3.26% H, 16.78% N, 12.76% S. IR spectrum (neat), cm⁻¹: 3430 (NH), 1716 (thioester), 1590 (Ph), 1494 (C=N), 1462 (OCH₃), 1404, 1255, 1180 (pyrazine). ¹H NMR (300 MHz, CDCl₃), : 9.90 (bs, 1H, NH), 8.80 (d, 1H, *J*=0.60 Hz, H3), 8.27 (d, 1H, *J*=0.60 Hz, H5), 7.32-7.25 (m, 2H, H2, H6), 7.15-7.06 (m, 3H, H3, H4, H5). ¹³C NMR (75 MHz, CDCl₃), : 161.8, 146.0, 145.7, 144.2, 142.2, 131.8, 130.2, 127.9, and 124.8.

4-Methoxyphenyl 5-chloropyrazine-2-carbothioimide (35). Generated along with nitrile **20**, method B as a by-product. Yield: 41%. *F_C* (EtOAc/petroleum ether 1:9) gave a light yellow oil. *R_F*: 0.50 (D). Anal. Calc. for C₁₂H₁₀ClN₃OS (279.75): 51.52% C, 3.60% H, 15.02% N, 11.46% S; found: 51.63% C, 3.71% H, 14.88% N, 11.35% S. IR spectrum (neat), cm⁻¹: 3432 (NH), 1709 (thioester), 1591 (Ph), 1490 (C=N), 1459 (OCH₃), 1394, 1259, 1166 (pyrazine). ¹H NMR (300 MHz, CDCl₃), : 9.93 (bs, 1H, NH), 8.98 (d, 1H, *J*=1.42 Hz, H3), 8.84 (d, 1H, *J*=1.42 Hz, H6), 7.55-7.50 (m AA'BB', 2H, H2', H6'), 7.16-7.10 (m AA'BB', 2H, H3', H5'), and 3.80 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 162.0, 161.5, 151.6, 144.8, 144.1, 143.6, 137.4, 118.2, 115.7, and 55.8.

3-Methoxyphenyl 5-chloropyrazine-2-carbothioimide (36). Generated along with nitrile **21**, method B as a by-product. Yield: 36%. *F_C* (EtOAc/petroleum ether 1:9) gave a light yellow oil. *R_F*: 0.48 (A). Anal. Calc. for C₁₂H₁₀ClN₃OS (279.75): 51.52% C, 3.60% H, 15.02% N, 11.46% S; found: 51.57% C, 3.65% H, 14.94% N, 11.41% S. IR spectrum (neat), cm⁻¹: 3435 (NH), 1713 (thioester), 1592 (Ph), 1495 (C=N), 1460 (OCH₃), 1387, 1253, 1165 (pyrazine). ¹H NMR (300 MHz, CDCl₃), : 9.90 (bs, 1H, NH), 8.95 (d, 1H, *J*=1.41 Hz, H3), 8.82 (d, 1H, *J*=1.41 Hz, H6), 7.42 (t, 1H, *J*=7.91 Hz, H5'), 7.25 (m, 1H, H6'), 7.22-7.15 (m, 1H, H2'), 7.07-7.00 (m, 1H, H4'), and 3.78 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 162.3, 160.3, 151.5, 144.5, 144.0, 143.6, 130.7, 129.8, 127.3, 119.8, 115.9, and 55.5.

4-Methoxyphenyl 3-chloropyrazine-2-carbothioimide (37). Generated along with nitrile **24**, method B as a by-product. Yield: 41%. *F_C* (EtOAc/petroleum ether 1:9) gave a light yellow oil. *R_F*: 0.67 (D). Anal. Calc. for C₁₂H₁₀ClN₃OS (279.75): 51.52% C, 3.60% H, 15.02% N, 11.46% S; found: 51.61% C, 3.68% H, 14.93% N, 11.33% S. IR spectrum (neat), cm⁻¹: 3432 (NH), 1712 (thioester), 1593 (Ph), 1491 (C=N), 1463 (OCH₃), 1404, 1253, 1178 (pyrazine). ¹H NMR (300 MHz, CDCl₃), : 9.81 (bs, 1H, NH), 8.72 (d, 1H, *J*=2.35 Hz, H6), 8.65 (d, 1H, *J*=2.35 Hz, H5), 7.53-7.49 (m AA'BB', 2H, H2', H6'), 7.02-6.97 (m AA'BB', 2H, H3', H5'), and 3.81 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), : 161.9, 160.5, 145.2, 144.9, 144.5, 142.6, 137.3, 118.1, 115.8, and 55.5.

3-Methoxyphenyl 3-chloropyrazine-2-carbothioimide (38). Generated along with nitrile **25**, method B as a by-product. Yield: 35%. *F_C* (EtOAc/petroleum ether 1:9) gave a light yellow oil. *R_F*: 0.51 (A). Anal. Calc. for C₁₂H₁₀ClN₃OS (279.75): 51.52% C, 3.60% H, 15.02% N, 11.46% S; found: 51.57% C, 3.65% H, 14.97% N, 11.39% S. IR spectrum (neat), cm⁻¹: 3434 (NH), 1714 (thioester), 1593 (Ph), 1494 (C=N), 1462 (OCH₃), 1403, 1250, 1179 (pyrazine). ¹H NMR (300 MHz, CDCl₃), : 9.77 (bs, 1H, NH), 8.70 (d, 1H, *J*=2.33 Hz, H6), 8.65 (d, 1H, *J*=2.33 Hz, H5), 7.34 (t, 1H, *J*=7.93 Hz, H5'), 7.16 (m, 1H, H6'), 7.09-7.06 (m, 1H, H2'),

6.99-6.92 (m, 1H, H^{4'}), and 3.78 (s, 3H, OCH₃). ¹³C NMR (75 MHz, CDCl₃), δ: 161.6, 160.5, 145.3, 144.8, 144.5, 142.5, 130.5, 129.8, 127.5, 119.7, 115.4, and 55.4.

2.3 Calculations

Ab initio (DFT) calculations (geometry optimisations, charge calculations) were performed in Gaussian 98W [31] Gaussian 03W [32] at the B3LYP/6-31+G(d) level [33]. Merz, Singh and Kollman procedure [34,35] was used for the calculation of the charges and polarizable conductor calculation (CPCM) solvation model [36], as implemented in Gaussian 98W [31], was used to simulate the DMF or gas medium and Gaussian [32] 03W was used to simulate the DMSO or EtOH medium. The dielectric constant of 38.3 was used for DMF.

During geometry optimisations, a systematic mapping over all exocyclic torsions (3 orientations for each) was performed (a PM3) [37,38] method, followed by the full B3LYP reoptimisation of the lowest-energy conformers). Atomic charges were calculated for the global minima found in this way.

3. RESULTS AND DISCUSSION

The main contribution of this paper is a novel 5-chloropyrazine-2-carbonitrile (**4**) regioselective preparation from pyrazine-2-carboxamide under the conditions described in Scheme 1. This modified preparation gave *N*-oxides of pyrazine-2-carboxamide mixture (**1a-c**) and subsequently regioisomers **3-5** in the opposite ratio than previously described, see Scheme 2 [17]. Nitriles **3-5** were identified on the basis of the comparison of NMR interaction constants with those reported [39].

As dehydration/chloration was performed under standard conditions [17], the key to the change of chloration regioselectivity was being searched for in *N*-oxide preparation. When the reaction conditions were changed, mixtures **1** and **2** should have contained different *N*-oxide isomer ratio, as shown according to the melting points (see Experimental), but, on the other hand, IR and ¹H, ¹³C NMR spectra of both mixtures **1**, **2** were identical. The spectra contained identical C-H vibrations [12] and chemical shifts (interaction constants) [8] for both mono *N*-oxides along with 1,4-dioxide. A HPLC separation of both mixtures **1,2**

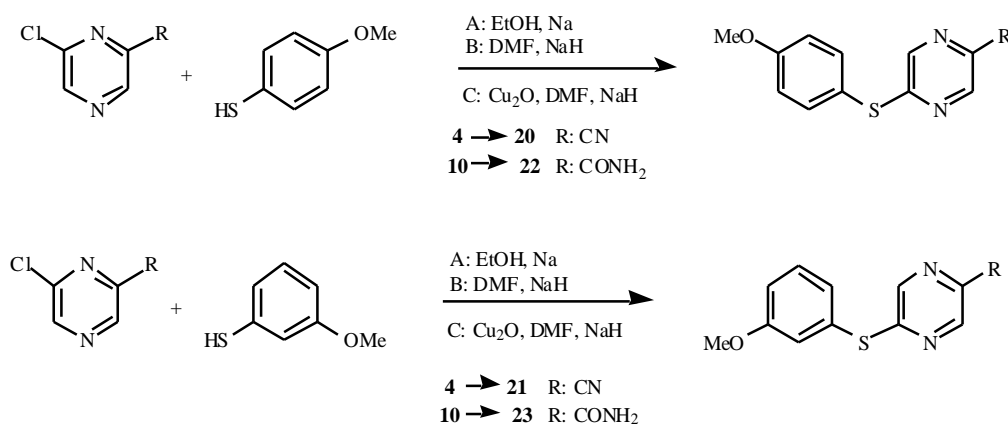
was performed (see Experimental), but both mixtures showed identical composition, see Table 4. Individual compounds were not identified, as the standards were not available.

These results were not precise (both mixtures showed identical content according to NMR spectra and HPLC analysis) due to a lower solubility of all analyzed samples. Nevertheless, in summary, mixtures **1** and **2** had different percentage contents according to the melting points and the isolated, fully characterized nitriles **3-5**.

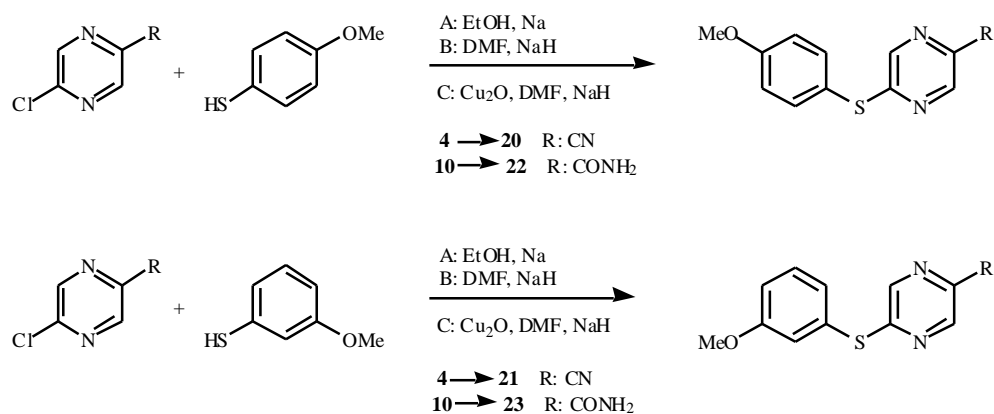
Intermediates **6-11** were prepared by well-known reactions, see Scheme 2. For the preparation of the ester of acid **6**, the method described in Scheme 2 had to be used. When esterification by methyl chlorosulfinate was applied [28], methyl 6-methoxypyrazin-2-carboxylate [29] (**30**) was obtained, see Scheme 6. 5-Chloropyrazine-2-carboxylic acid was prepared neither by nitrile **4** nor amide **10** hydrolysis (acid/alkaline). Sato prepared this acid only by 5-(2-furyl)-2-chloropyrazine decomposition [40]. Due to their decomposition, 5-[(4-methoxyphenyl)sulfanyl]- and 5-[(3-methoxyphenyl)sulfanyl]pyrazine-2-carboxylic acids were not prepared by the hydrolysis of nitriles **20**, **21** or amides **22**, **23**, either.

Subsequently, compounds **3-11** were treated with arylthiolates to give sulphides **12-29**, see Schemes 3-5. Interesting by-products (thioimidates **32-38**) were formed in the reaction of nitriles **3-5** with arylthiols under specific conditions (Scheme 6).

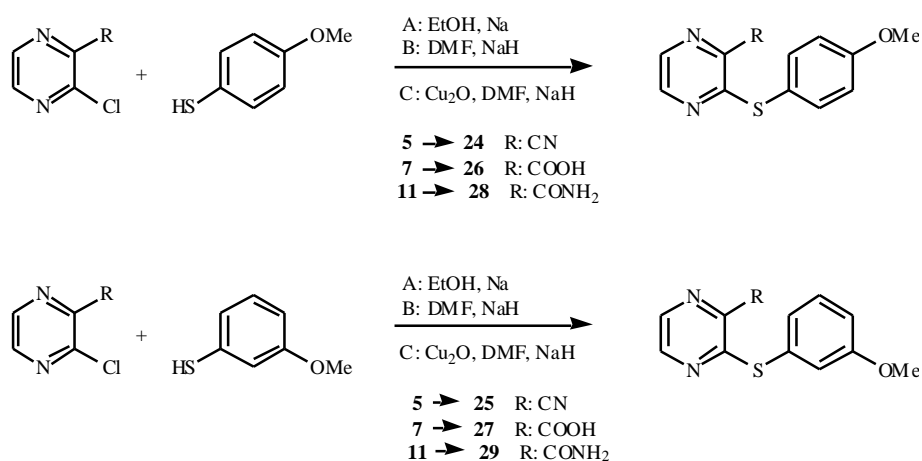
Foks [25] and Doležal [20] prepared various substituted 6-(phenylsulfanyl)pyrazine-2-carbonitrile derivatives in EtOH/EtONa in 85% yield. Therefore, coupling of nitriles **3-5** with 4- or 3-methoxybenzene-1-thiols was performed under the same conditions, but in only 51-74% yields. Thus, the aim of our work was to increase the yields of this nucleophilic substitution and to propose a reaction mechanism. Coupling of compounds **3-11** was performed under different conditions (methods A, B, C, see Schemes 3-5) and the reactivity of compounds **3-11** was correlated to the calculated values of electronic deficiency in positions C₍₆₎ (Table 1), C₍₅₎ (Table 2) and C₍₃₎ (Table 3) of the pyrazine ring. *Ab initio* point charges calculated in Gaussian 98W [31] Gaussian 03W [32] and adjusted to electrostatic potential were used as a measure of electronic deficiency. A



Scheme 3. Nucleophilic coupling of 6-chloropyrazine-2-carboxylic acid derivatives.



Scheme 4. Nucleophilic coupling of 5-chloropyrazine-2-carboxylic acid derivatives.



Scheme 5. Nucleophilic coupling of 3-chloropyrazine-2-carboxylic acid derivatives.

Table 4. Retention times and percentage content of separate compounds in the mixtures 1 and 2, which were evaluated by means of internal normalization of areas method.

Mixture 1		Mixture 2	
Retention time [min]	Content [%]	Retention time [min]	Content [%]
6.27	27.0	6.27	26.4
7.47	33.9	7.47	34.0
8.14	34.6	8.14	34.7
10.38 – pyrazinamide	3.6	10.38 – pyrazinamide	3.8
Another contaminant	0.9	Another contaminant	1.1

formal charge of 0 corresponds to a radical structure. The values for a non-radical intermediate are also included; in that case, the formal charge of a molecule must be +1.

The differences in the charges were smaller than we expected, and the correlation between the values and yields was not explicit. All charges correspond to a DMF and EtOH solutions. The presence of a solvent (DMF, EtOH), however, had only a negligible effect on the calculated charge values, as proved by gas-phase calculations, with the exception of the radical generated from amide **9** and the cation from amide **11**, see Table 5. The charges were also quite insensitive to geometries, as verified with some other local

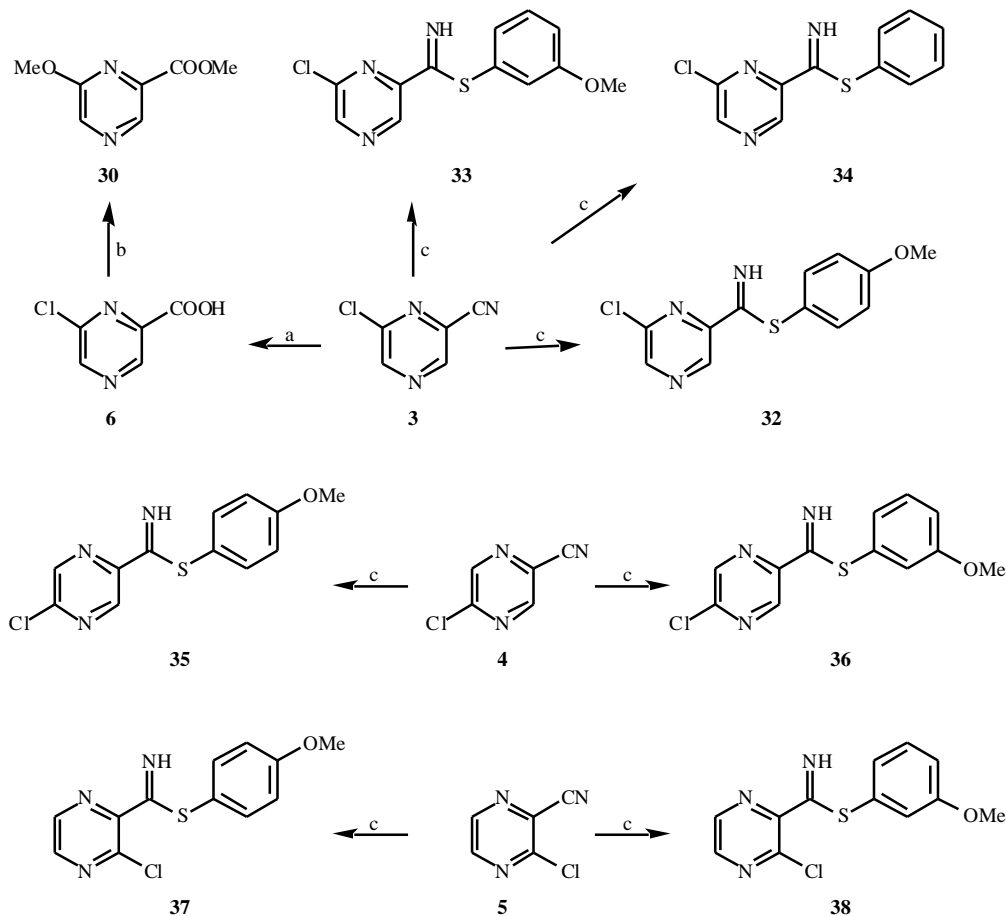
minima structures. In spite of this fact, we can only speculate that some other factors came into play in the course of the coupling reaction. Nevertheless, the experimentally observed trends are much better interpreted assuming the radical intermediate, which supports the proposed mechanism, see Scheme 7.

The coupling performed in EtOH/EtONa (method A) produced different yields depending on the chlorine position (C₅ being the most reactive) and on the functional group attached to the pyrazine ring (decreasing reactivity: nitrile > acid > ester > amide) and on the quality of methoxybenzenethiol used. Bis(4-methoxyphenyl)disulfide

Table 5. Difference in charges of 6- or 5- or 3-chloropyrazine-2-carboxamide in different media. Calculations were performed in gas medium and DMF (Gaussian 98W) and in EtOH and DMSO (Gaussian 03W) [31,32]. Quite different charges of reaction intermediates generated from **9**, **11** were not explained. The difference in charges of reaction intermediates generated from **10** in all discussed media was insignificant.

Reactant	Medium							
	Gas		DMF		DMSO		EtOH	
	Radical ^a	Cation ^b	Radical ^a	Cation ^b	Radical ^a	Cation ^b	Radical ^a	Cation ^b
9	-0.26	0.32	-0.45	0.35	-0.27	0.40	-0.27	0.39
10	-0.11	0.33	-0.12	0.37	-0.12	0.44	-0.12	0.43
11	-0.10	0.26	-0.18	0.25	-0.17	0.66	-0.16	0.66

^a atomic charges at a former position of the chlorine in reactant, formal charge of a molecule 0, ^b *ibid.*, formal charge +1.



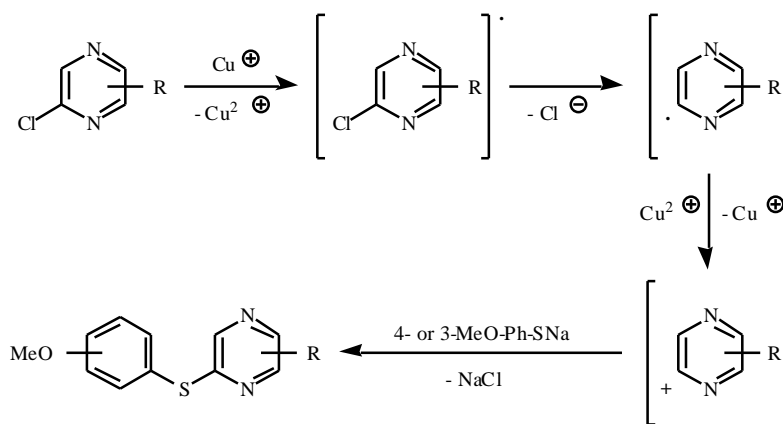
Scheme 6. By-products generated from 6-chloropyrazine-2-carbonitrile (**3**) or 6-chloropyrazine-2-carboxylic acid (**6**) and from 5-chloropyrazine-2-carbonitrile (**4**) and 3-chloropyrazine-2-carbonitrile (**5**).

(**31**) was formed from 4-methoxybenzene-1-thiol up to 26% in EtOH, but bis(3-methoxyphenyl)disulfide was not detected (methoxy group in an unsymmetrical position decreased sulfanyl group reactivity, but an increased antioxidation/dehydrogenation resistance simultaneously). The substitution with the more reactive 4-methoxybenzene-1-thiol gave lower yields due to disulfide **31** production than the coupling with the less reactive 3-methoxybenzene-1-thiol.

The coupling performed in DMF (method B) gave low yields of the products (destruction of the pyrazine substrates with the exception of acids **6** and **7**; therefore, the reaction

was terminated after 1 h), and moderate yields of disulfide **31** (30%). Methoxyphenyl chloropyrazine-2-carbothioimides (**32-38**) were formed from nitriles **3-5** in 36-41% yields (Scheme 6), but compounds of the 4-methoxyphenyl-6-[(4-methoxyphenyl)sulfanyl]pyrazine-2-carbothioimide type were not isolated.

The highest yields were obtained under catalysis by powdered heterogeneous copper(I) oxide (method C). The use of this catalyst resulted from our previous studies [21,22,30]. The reactivity of individual thiols was balanced (disulfide **31** negligible yields via reductive effect of the catalyst). Differences in the yields depended on the chlorine



Scheme 7. The general radical-ionic mechanism of nucleophilic coupling allowed through heterogeneous copper catalysts in polar aprotic solvents, respectively. Pyrazinyl radical anions and changes in the oxidation numbers of copper catalyst are showed.

position (C₅) being the most reactive) and on the functional group (decreasing reactivity: nitrile > acid > ester > amide).

6-Phenylsulfanylpyrazine-2-carbonitrile (**14**) [25] was synthesized in order to verify the conclusions that were made. Benzenethiol was chosen due being ring of substituents. Consequently, the compound should have a higher reactivity than 3-methoxybenzene-1-thiol and lower than 4-methoxybenzene-1-thiol, and hence nitrile **3** reactivity should not be influenced by disulfide generation. This assumption was correct, see Table 6. Diphenyldisulfide was not isolated.

Table 6. Conditions and yields of 6-chloropyrazin-2-carbonitrile (3) coupling with benzenethiol. (A: EtOH, Na, 3 h; B: DMF, NaH, 1 h; C: Cu₂O, DMF, NaH, 20 min).

Reactant	Product	Conditions	Yield [%]
3	14	dioxan, 15 min	90 [25]
3	14	A	69
		B	38, (34 38%)
		C	92

The disulfide generation or the ability of individual thiols used to resist oxidation/dehydrogenation was correlated with the calculated values of the charges on sulphur in the thiolate form in the gas medium (4-methoxybenzene-1-thiol: -0.82; benzenethiol: -0.81; 3-methoxybenzene-1-thiol: -0.78). *Ab initio* point charges were calculated in Gaussian 98W [31]. According to the assumption, DFT calculations and Hammett constants (ρ_m : 0,12 ρ_p : -0,27 for -OCH₃) [41], we can conclude, that the presence of the methoxy group in the *meta* position in the benzenethiolate anion leads to a lower nucleophilicity of the anion in the coupling process, but also to a higher oxidation/dehydrogenation resistance.

CONCLUSIONS

All newly prepared compounds were characterised by ¹H, ¹³C NMR spectra, IR spectra, and by means of CHN analysis. New regiospecific preparation of 5-chloropyrazine-2-carbonitrile from pyrazinamide was described with the yield of 54%. Convenient conditions for the coupling of chloropyrazine-2-carboxylic acid derivatives with

methoxybenzenethiols were described and radical-ionic mechanism of the substitution, catalyzed by heterogeneous copper catalyst, was proposed. These conditions gave higher yields than the conditions previously described [14,25]. 5-Chloropyrazine-2-carboxylic acid derivatives showed the highest reactivity. 6- or 3-Chloropyrazine-2-carboxylic acid derivatives displayed a comparable and lower reactivity.

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