Chemistry of Heterocyclic Compounds, Vol. 42, No. 10, 2006

SYNTHESES OF NEW 1,2-, 1,3-, AND 1,4-DIAZINE DERIVATIVES. 2*. HYDROLYSIS AND ALKYLATION OF DIAZINYLPHENYLACETONITRILES

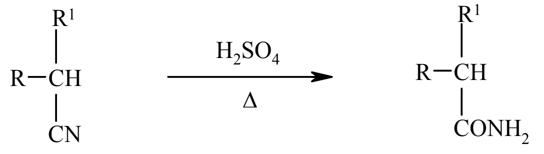
K. Wisterowicz and H. Foks

A number of aryldiazinyl acetonitriles were subjected to hydrolysis, methylation, and benzylation reactions. They resulted in the formation of aryldiazinylacetamides, diazinylmethylacetonitriles, and benzyldiazinylacetonitriles, respectively.

Keywords: 2-benzylpyrazines, diazinylphenylacetamides, diazinylphenylacetonitriles, alkylation, hydrolysis, decarboxylation.

The continuation of previously reported syntheses of new pyridazine, pyrimidine, and pyrazine derivatives containing an active methine fragment [1] is described in the present paper.

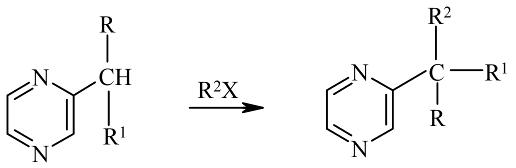
Aryldiazinylacetonitriles were the substrates subjected to hydrolysis action of concentrated sulfuric acid. This gave a series of aryldiazinylacetamides, as shown below:



$$\mathrm{R-\underset{CN}{\overset{R^1}{CH}}} \xrightarrow[\Delta]{H_2SO_4} \mathrm{R-\underset{CONH_2}{\overset{R^1}{CH}}}$$

1–10

Diazinylacetonitrile derivatives with unsubstituted methine hydrogen atom were then exposed to methylation and benzylation reactions. These proceeded in 50% aqueous sodium hydroxide/dimethyl sulfoxide medium under the action of methyl iodide in methylation, and benzyl chloride in benzylation reactions, respectively. The diazinylmethylacetonitriles **11, 12** and diazinylbenzylacetonitriles **13-15** were the products obtained, as shown below:



11–15

---

[*] For Communication 1, see [1].

Department of Organic Chemistry, Medical University of Gdansk, 80-416 Gdansk, Poland; e-mail: hfoks@amg.gda.pl. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1534-1540, October, 2006. Original article submitted January 25, 2005; revision submitted June 8, 2006.

TABLE 1. Characteristics of the Newly Synthesized Compounds **1-10**

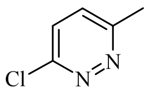
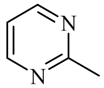
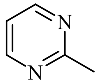
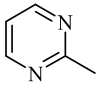
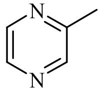
Compound	R	R^1	Empirical formula	Found, % / Calculated, %			mp, °C (solvent for crystalization)	Yield, %
				C	H	N		
1	2	3	4	5	6	7	8	9
1		2,4-$Cl_2C_6H_3$	$C_{12}H_8Cl_3N_3O$	$\frac{45.53}{45.38}$	$\frac{2.55}{2.46}$	$\frac{13.27}{13.38}$	69-70 (MeOH)	47
2		4-ClC_6H_4	$C_{12}H_{10}ClN_3O$	$\frac{58.19}{58.02}$	$\frac{4.07}{4.27}$	$\frac{16.96}{17.12}$	125-128 (MeOH)	19
3		2,4-$Cl_2C_6H_3$	$C_{12}H_9Cl_2N_3O$	$\frac{51.09}{50.97}$	$\frac{3.22}{3.36}$	$\frac{14.89}{14.76}$	178-182 (PrOH)	78
4		3,4-$(MeO)_2C_6H_3$	$C_{14}H_{15}N_3O_3$	$\frac{61.53}{61.36}$	$\frac{5.53}{5.68}$	$\frac{15.38}{15.52}$	149-153 (petroleum ether)	31
5		2,4-$Cl_2C_6H_3$	$C_{12}H_9Cl_2N_3O$	$\frac{51.09}{50.86}$	$\frac{3.22}{3.41}$	$\frac{14.89}{15.10}$	178-181 (MeOH)	41

TABLE 1 (continued)

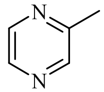
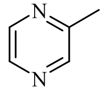
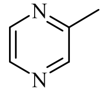
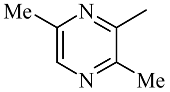
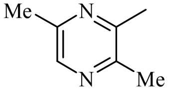
1	2	3	4	5	6	7	8	9
6		3,4-$Cl_2C_6H_3$	$C_{12}H_9Cl_2N_3O$	$\frac{51.09}{50.96}$	$\frac{3.22}{3.37}$	$\frac{14.89}{15.14}$	170-174 ($CHCl_3$)	55
7		2,6-$Cl_2C_6H_3$	$C_{12}H_9Cl_2N_3O$	$\frac{51.09}{50.88}$	$\frac{3.22}{3.46}$	$\frac{14.89}{14.97}$	154-157 (MeOH)	10
8		2-Naphthyl	$C_{16}H_{13}N_3O$	$\frac{72.99}{72.86}$	$\frac{4.97}{5.12}$	$\frac{15.96}{16.14}$	360 (MeOH)	78
9		3,4-$Cl_2C_6H_3$	$C_{14}H_{13}Cl_2N_3O$	$\frac{54.21}{54.06}$	$\frac{4.22}{4.48}$	$\frac{13.55}{13.78}$	225-227 (MeOH)	30
10		2,6-$Cl_2C_6H_3$	$C_{14}H_{13}Cl_2N_3O$	$\frac{54.21}{54.30}$	$\frac{4.22}{4.50}$	$\frac{13.55}{13.69}$	205-208 (MeOH)	15

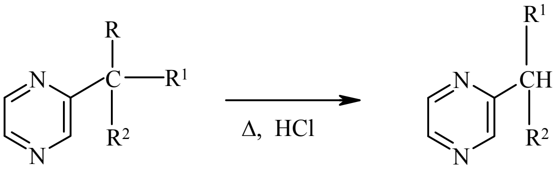
TABLE 2. IR and ^{1}H NMR data for compounds **1-10**

Compound	IR spectrum, cm^{-1}	^{1}H NMR spectrum, δ, ppm*
1	1700 (C=O), 3070 (CH aromatic), 3340 (NH_2)	7.50 (5H, m, 2H pyridazine and 3H phenyl); 5.75 (1H, s, CH)
2	1660 (C=O), 2960 (CH alkyl), 3060 (CH aromatic), 3380, 3330 (NH_2)	6.90 (3H, m, pyrimidine); 5.90 (4H, m, phenyl); 4.50 (1H, s, CH)
3	1660 (C=O), 2940 (CH alkyl), 3050 (CH aromatic), 3420, 3240 (NH_2)	7.50 (6H, m, 3H pyrimidine and 3H phenyl); 5.50 (1H, s, CH); 4.20 (2H, s, NH_2)
4	1680 (C=O), 2960 (CH alkyl), 3080 (CH aromatic), 3350 (NH_2)	6.90 (3H, m, pyrimidine); 5.70 (3H, m, phenyl); 4.15 (1H, s, CH); 3.10 (6H, s, $2CH_3$)
5	1650 (C=O), 2940 (CH alkyl), 3060 (CH aromatic), 3360 (NH_2)	6.90 (3H, m, pyrazine); 6.05 (3H, m, phenyl); 4.40(1H, s, CH); 2.75 (2H, s, NH_2)
6	1670 (C=O), 2930 (CH alkyl), 3060 (CH aromatic), 3340 (NH_2)	6.90 (3H, m, pyrazine); 6.10 (3H, m, phenyl); 4.20 (1H, s, CH)
7	1680 (C=O), 2920 (CH alkyl), 3020 (CH aromatic), 3340 (NH_2)	6.90 (3H, m, pyrazine); 5.90 (3H, m, phenyl); 4.70 (1H, s, CH)
8	1650 (C=O), 2980 (CH alkyl), 3080 (CH aromatic), 3380 (NH_2)	6.80 (3H, m, pyrazine); 6.10 (7H, m, naphthyl); 4.30 (1H, s, CH); 2.75 (2H, s, NH_2)
9	1690 (C=O), 2960 (CH alkyl), 3060 (CH aromatic), 3320 (NH_2)	6.65 (1H, s, pyrazine); 5.95 (3H, m, phenyl); 4.25 (1H, s, CH); 2.70 (2H, s, NH_2); 2.0(6H, m, 2 CH_3)
10	1680 (C=O), 2960 (CH alkyl), 3050 (CH aromatic), 3330 (NH_2)	6.60 (1H, s, pyrazine); 5.80 (3H, m, phenyl); 4.70 (1H, s, CH); 1.90 (6H, s, $2CH_3$)

---

* Compounds **1**, **2**, **4**, **7**, **10** – in $CDCl_3$, compounds **3**, **5**, **6**, **8**, **9** – in DMSO-d_6.

Some pyrazinylacetonitriles, *viz.* 4-chlorophenyl-2-pyrazinylacetonitrile, 3',4'-dichlorophenyl-2-pyrazinylacetonitrile, 2'-naphthyl-2-pyrazinylacetonitrile (syntheses described in [1]), as well as compounds **14** and **15** were subjected to hydrolysis, followed by decarboxylation. These reactions gave 2-benzylpyrazine derivatives **16-20**, as shown below:



16–20

The yields, physical properties of the reactions as well as the results of IR and ^{1}H NMR spectral analyses are given in Tables 1, 2 (for compounds **1-10**), and 3, 4 (for compounds **11-20**).

EXPERIMENTAL

Melting points were determined with a Boetius apparatus and are uncorrected. The IR spectra were taken with a Satellite spectrophotometer (KBr pellets), and ^{1}H NMR spectra – with a Varian Gemini 200 apparatus (200 MHz) with TMS as an internal standard.

Syntheses of Diazinylacetamides 1-10. (General Method). 2,4-Dichlorophenylpyrazinylacetonitrile (0.53 g, 2 mmol) was heated on the water bath with concentrated H_2SO_4 (1.9 ml) for 10 min. Then the reaction

TABLE 3. Characteristics of the Newly Synthesized Compounds **11-20**

Compound*	R^1	R^2	Empirical formula	Found, % / Calculated, %			mp, °C (solvent for crystalization)	Yield, %
				C	H	N		
11	4-ClC_6H_4	Me–	$C_{13}H_{10}ClN_3$	64.07 63.88	4.14 4.28	17.24 17.46	65-68 (MeOH)	22
12	2-Naphthyl	Me–	$C_{17}H_{13}N_3$	78.74 78.56	5.05 5.18	16.20 16.46	72-74 (MeOH)	34
13	4-ClC_6H_4	$PhCH_2$–	$C_{19}H_{14}ClN_3$	71.36 71.12	4.41 4.63	13.13 13.38	83-84 (MeOH)	40
14	2,4-$Cl_2C_6H_3$	$PhCH_2$–	$C_{19}H_{13}Cl_2N_3$	64.42 64.18	3.70 3.86	11.86 11.98	118-128 (MeOH)	36
15	2-Naphthyl	$PhCH_2$–	$C_{23}H_{17}N_3$	82.36 82.10	5.10 5.36	12.53 12.71	112-115 (MeOH)	50
16	4-ClC_6H_4	H	$C_{11}H_9ClN_2$	64.56 64.38	4.43 4.65	13.69 13.82	46-49 (dioxane)	39
17	3,4-$Cl_2C_6H_3$	H	$C_{11}H_8Cl_2N_2$	55.26 55.07	3.37 3.48	11.72 11.93	50-52 (MeOH–H_2O)	28
18	2-Naphthyl	H	$C_{15}H_{12}N_2$	81.79 81.52	5.49 5.57	12.71 12.96	68-70 (MeOH)	34
19	2,4-$Cl_2C_6H_3$	$PhCH_2$–	$C_{18}H_{14}Cl_2N_2$	65.67 65.46	4.29 4.47	8.50 8.73	80-82 (MeOH)	46
20	2-Naphthyl	$PhCH_2$–	$C_{22}H_{18}N_2$	85.13 85.02	5.86 6.04	9.02 9.27	106-108 (MeOH)	45

---

* Compounds **11-20** R = CN.

TABLE 4. IR and ^{1}H NMR Data for Compounds **11-20**

Compound	IR spectrum, cm^{-1}	^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)
11	3100 (CH aromatic), 2980, 2940 (CH alkyl), 2250 ($C\equiv N$)	7.10 (1H, s, pyrazine); 6.99 (2H, s, pyrazine); 6.05 (4H, m, phenyl); 1.80 (3H, s, CH_3)
12	3090 (CH aromatic), 2940 (CH alkyl), 2270 ($C\equiv N$)	7.00 (3H, m, pyrazine); 6.40, 6.10 (7H, m, 4H and 3H naphthalene); 1.85 (3H, s, CH_3)
13	3040 (CH aromatic), 2960, 2920 (CH alkyl), 2260 ($C\equiv N$)	7.00 (3H, m, pyrazine); 6.65 (9H, m, phenyl); 2.70 (2H, s, CH_2)
14	3080 (CH aromatic), 2980, 2920 (CH alkyl), 2260 ($C\equiv N$)	6.85 (3H, m, pyrazine); 5.90 (8H, m, phenyl); 2.70 (2H, s, CH_2)
15	3060 (CH aromatic), 2960, 2920 (CH alkyl), 2260 ($C\equiv N$)	7.00 (3H, m, pyrazine); 6.40, 6.10, 5.70 (12H, m, 5H phenyl and 7H naphthalene); 2.70 (2H, s, CH_2)
16	3040 (CH aromatic), 2980, 2920 (CH alkyl), 1580, 1540, 1500 (phenyl ring)	6.90 (3H, m, pyrazine); 5.95 (4H, m, phenyl); 2.70 (2H, s, CH_2)
17	3100 (CH aromatic), 2940, 2880 (CH alkyl), 1590, 1540, 1500 (phenyl ring)	6.80 (3H, m, pyrazine); 5.95 (3H, m, phenyl); 2.70 (2H, s, CH_2)
18	3080(CH aromatic), 2940, 2880(CH alkyl), 1590, 1550, 1440(phenyl ring)	6.90 (3H, m, pyrazine); 6.40, 6.00 (7H, m, naphthalene); 2.70 (2H, s, CH_2)
19	3100 (CH aromatic), 2980, 2940 (CH alkyl), 1640, 1540, 1490 (phenyl ring)	6.90 (3H, m, pyrazine); 5.85 (8H, m, phenyl); 3.95 (1H, m, CH); 2.70 (2H, s, CH_2)
20	3080 (CH aromatic), 2940, 2880 (CH alkyl), 1600, 1540, 1490 (phenyl ring)	6.85 (3H, m, pyrazine); 6.15, 5.70 (12H, m, naphthalene and phenyl); 3.85 (1H, m, CH); 2.70 (2H, s, CH_2)

mixture was poured into ice water and alkalized with 25% aqueous ammonia. The precipitated product was crystallized from methanol. Compound **5** (0.23g, mp 179-181°C) was obtained; compounds **1-4** and **6-10** were obtained analogously.

Syntheses of Diazinylmethylacetonitriles and Diazinylbenzylacetonitriles 11-15. (General Method). To 2-naphthylopyrazinylacetonitrile (0.49 g, 2 mmol) DMSO (1 ml), methyl iodide (0.2 ml, 2 mmol), and 50% aqueous NaOH (0.5 ml) were added. The whole was heated on the water bath at 70°C for 1 h with vigorous stirring. Then the reaction mixture was poured into ice water, acidified with concentrated HCl to pH 3, and extracted thrice with chloroform. The extracts were dried with anhydrous $MgSO_4$ and thickened under reduced pressure. The residue was crystallized from methanol. Compound **12** was obtained (0.18 g). Compounds **11** and **13-15** were obtained analogously.

Syntheses of Benzylpyrazines 16-20. (General Method). To 2-(4'-chlorophenyl)cyanomethylpyrazine (0.5 g, 2 mmol) concentrated HCl (5 ml) was added and the whole heated for 5 h. Then the reaction mixture was poured into ice water, alkalized with 25% aqueous ammonia and extracted thrice with chloroform. The extract was evaporated to dryness under vacuum and the residue crystallized from diethyl ether. Compound **16** (0.36 g) was obtained. Other benzylpyrazines **17-20** were obtained analogously.

REFERENCES

1. K. Wisterowicz and H. Foks, *Khim. Geterotsikl. Soedin.*, 1346 (2006). [*Chem. Heterocycl. Comp.*, **42**, 1168 (2006)].