Chemistry of Heterocyclic Compounds, Vol. 42, No. 9, 2006

SYNTHESES OF NEW 1,2-, 1,3-, AND 1,4-DIAZINE DERIVATIVES. 1. SYNTHESIS OF DIAZINYLARYLACETONITRILES

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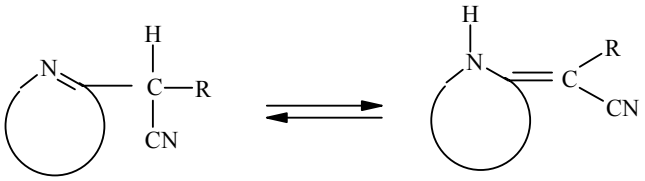
A number of diazinylarylacetonitriles were obtained in the reactions of properly substituted 3-chloropyridazine, 2-chloropyrimidine, or 2-chloropyrazine derivatives with various arylacetonitriles.

Keywords: chlorodiazines, diazynylphenylacetonitriles, phenylacetonitriles, phase-transfer synthesis.

The syntheses of heterocyclic compounds with an active methine fragment in α-position to the nitrogen atom are described in the present paper.

Compounds of this kind are of interest from both pharmaceutical and chemical points of view. As they have an unsubstituted hydrogen atom, the existence of two tautomeric forms – the so-called CH- and NH-acids – is possible (Scheme 1).

Scheme 1



The tautomerism arising from the mobile methine proton migration towards the heterocyclic nitrogen atom was examined by many authors [1-4].

The compounds having an active methine fragment appear to be biologically active, too. Some of them are analgesic and antiphlogistic [5-6]; others affect the secretion of gastric juices [7] or exhibit affinity to dopamine receptors [8].

Attempts to synthesize the 1,2-, 1,3-, and 1,4-diazine derivatives were aimed at obtaining some new potentially active therapeutics. The diazines, *viz*., 3,6-dichloropyridazine, 3-chloro-6-methoxypyridazine, 2-chloropyrimidine, 2,4-dichloropyrimidine, 2-chloropyrazine, and 3-chloro-2,5-dimethylpyrazine, were used as substrates in reactions with the following substituted phenylacetonitriles: 3-chloro-, 4-chloro-, 2,4-dichloro-, 2,6-dichloro-, 3,4-dichloro-, 4-hydroxy-, 3,4-dimethoxy-, and 3,4,5-trimethoxyphenylacetonitrile. The reactions proceeded in a biphase system of 50% aqueous sodium hydroxide – dimethylsulfoxide. The ^{1}H NMR spectra showed that in this system the derivatives obtained had the structure of CH-acids. The reactions course is shown in Scheme 2.

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TABLE 1. Characteristics of the Newly Synthesized Compounds

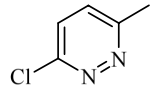
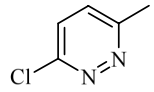
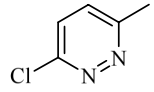
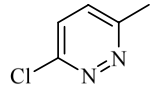
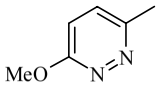
Compound	R	R^1	Empirical formula	Found, % / Calculated, %			mp, °C (solvent for crystalization)	Yield, %
				C	H	N		
1	2	3	4	5	6	7	8	9
1		2,4-$Cl_2C_6H_3$	$C_{12}H_6Cl_3N_3$	48.28 / 48.13	2.03 / 2.21	14.07 / 14.26	110-112 (MeOH)	43
2		3,4,5-$(MeO)_3C_6H_2$	$C_{15}H_{14}ClN_3O_3$	56.36 / 56.07	4.41 / 4.12	13.14 / 13.28	107-110 (*i*-PrOH)	28
3		2-Naphthyl	$C_{16}H_{10}ClN_3$	68.70 / 68.56	3.60 / 3.72	12.67 / 12.93	135-138 (H_2O)	10
4		2-Pyridyl	$C_{11}H_7ClN_4$	57.28 / 57.40	3.06 / 3.12	24.29 / 24.41	236-238 (dioxane)	41
5		4-ClC_6H_4	$C_{13}H_{10}ClN_3O$	60.13 / 60.02	3.88 / 3.76	16.18 / 16.24	136-138 (cyclohexane)	12

TABLE 1 (continued)

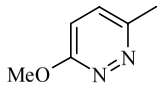
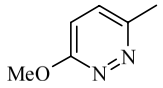
1	2	3	4	5	6	7	8	9
6		3,4-$Cl_2C_6H_3$	$C_{13}H_9Cl_2N_3O$	53.08 53.24	3.08 2.96	14.29 14.42	148-150 (*i*-PrOH)	35
7		2,6-$Cl_2C_6H_3$	$C_{13}H_9Cl_2N_3O$	53.08 53.12	3.08 3.27	14.29 14.41	183-186 (cyclohexane)	20
8		3-ClC_6H_4	$C_{12}H_8ClN_3$	62.76 62.52	3.51 3.66	18.30 18.41	101-103 (MeOH)	15
9		4-ClC_6H_4	$C_{12}H_8ClN_3$	62.76 62.83	3.51 3.72	18.30 18.42	76-78 (*i*-PrOH)	42
10		2,4-$Cl_2C_6H_3$	$C_{12}H_7Cl_2N_3$	54.57 54.71	2.67 2.74	15.91 16.16	93-95 (*i*-PrOH)	58
11		3,4-$(MeO)_2C_6H_3$	$C_{14}H_{13}N_3O_2$	65.87 65.63	5.13 5.27	16.46 16.63	165-168 (*i*-PrOH)	40

TABLE 1 (continued)

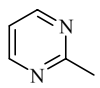
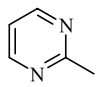
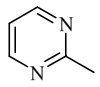
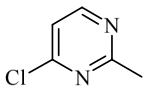
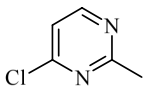
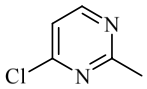
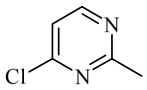
1	2	3	4	5	6	7	8	9
12		3,4,5-$(MeO)_3C_6H_2$	$C_{15}H_{15}N_3O_3$	63.15 63.02	5.30 5.45	14.73 14.91	124-126 (*i*-PrOH)	46
13		2-Naphthyl	$C_{16}H_{11}N_3$	78.35 78.15	4.52 4.64	17.13 17.28	90-94 (EtOH–H_2O)	29
14		2-Pyridyl	$C_{11}H_8N_4$	67.34 67.11	4.11 4.29	28.55 28.73	168-169 (*i*-PrOH)	18
15		4-ClC_6H_4	$C_{12}H_7Cl_2N_3$	54.57 54.38	2.67 2.77	15.90 16.12	115-118 (MeOH)	42
16		3,4-$Cl_2C_6H_3$	$C_{12}H_6Cl_3N_3$	48.28 48.02	2.03 2.15	14.07 14.31	192-195 (MeOH)	55
17		2,6-ClC_6H_3	$C_{12}H_6Cl_3N_3$	48.28 48.13	2.03 2.25	14.07 14.13	300-303 (MeOH)	56
18		3,4-$(MeO)_2C_6H_3$	$C_{14}H_{12}ClN_3O_2$	58.04 57.86	4.17 4.10	14.50 14.78	203-206 (dioxane–H_2O)	17

TABLE 1 (continued)

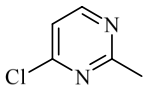
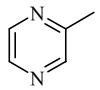
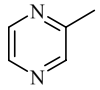
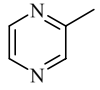
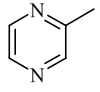
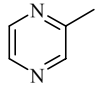
1	2	3	4	5	6	7	8	9
19		2-Pyridyl	$C_{11}H_7ClN_4$	57.28 57.01	3.06 3.26	24.29 24.35	216-218 (MeOH)	27
20		3-ClC_6H_4	$C_{12}H_8ClN_3$	62.76 62.17	3.51 3.43	18.30 18.48	96-98 (EtOH–H_2O)	34
21		4-ClC_6H_4	$C_{12}H_8ClN_3$	62.76 62.63	3.51 3.35	18.30 18.49	103-107 (EtOH–H_2O)	48
22		2,4-$Cl_2C_6H_3$	$C_{12}H_7Cl_2N_3$	54.57 54.43	2.67 2.86	15.91 16.14	69-70 (*i*-PrOH)	26
23		3,4-$Cl_2C_6H_3$	$C_{12}H_7Cl_2N_3$	54.57 54.36	2.67 2.79	15.91 16.14	113-115 (H_2O)	41
24		2,6-$Cl_2C_6H_3$	$C_{12}H_7Cl_2N_3$	54.57 54.33	2.67 2.39	15.91 16.33	94-95 (MeOH–H_2O)	45

TABLE 1 (continued)

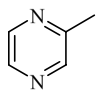
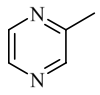
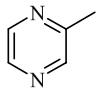
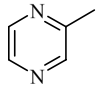
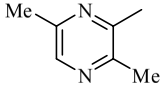
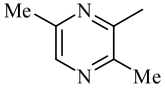
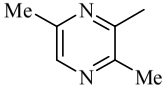
1	2	3	4	5	6	7	8	9
25		4-$MeOC_6H_4$	$C_{13}H_{11}N_3O$	69.32 69.08	4.92 5.15	18.65 18.89	132-136 (petroleum ether)	20
26		3,4-$(MeO)_2C_6H_3$	$C_{14}H_{13}O_2N_3$	65.87 65.63	5.13 5.29	12.53 12.80	119-123 (EtOH)	12
27		2-Naphthyl	$C_{16}H_{11}N_3$	78.35 78.08	4.52 4.37	17.13 17.10	56-59 (EtOH–H_2O)	20
28		2-Pyridyl	$C_{11}H_8N_4$	67.34 67.26	4.10 4.22	28.55 28.72	191-193 (EtOH)	52
29		3,4-$Cl_2C_6H_3$	$C_{14}H_{11}Cl_2N_3$	57.55 57.38	3.79 3.86	14.38 14.51	93-95	58
30		2,6-$Cl_2C_6H_3$	$C_{14}H_{11}Cl_2N_3$	57.55 57.46	3.79 3.91	14.38 14.61	87-90	51
31		3,4-$(MeO)_2C_6H_3$	$C_{16}H_{17}N_3O_2$	67.82 67.70	6.05 6.18	14.83 14.97	110-112 (dioxane–H_2O)	29

TABLE 2. IR and ^{1}H NMR Data for Compounds **1-31**

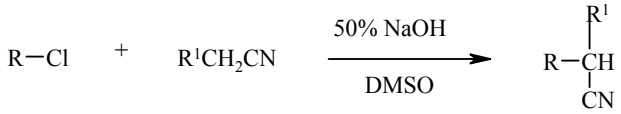
Com-pound	IR spectrum, cm^{-1}	^{1}H NMR spectrum, δ, ppm*
1	2	3
1	3100 (CH aromatic), 2980, 2940 (CH alkyl), 2270 (C≡N), 1590, 1540, 1480 (phenyl ring)	7.50 (5H, m, 2H pyridazine and 3H phenyl); 5.90 (1H, s, CH)
2	3080 (CH aromatic), 2980, 2940 (CH alkyl), 2260 (C≡N), 1600, 1540, 1480 (phenyl ring)	7.70 (4H, m, 2H pyridazine and 2H phenyl); 6.30 (1H, s, CH); 3.80 (9H, m, $3CH_3$)
3	3080 (CH aromatic), 2980, 2940 (CH alkyl), 2260 (C≡N), 1590, 1550, 1500 (phenyl ring)	7.75 (9H, m, 2H pyridazine and 7H naphthalene); 5.85 (1H, s, CH)
4	3100 (CH aromatic), 2220 (C≡N), 1600, 1580, 1540 (phenyl ring)	7.40 (6H, m, 2H pyridazine + 4H pyridine); 1.65 (1H, s, CH)
5	3070 (CH aromatic), 2990, 2950 (CH alkyl), 2252 (C≡N), 1595, 1550, 1492 (phenyl ring)	7.40 (6H, m, 2H pyridazine and 4H phenyl); 5.55 (1H, s, CH); 4.15 (3H, s, CH_3)
6	3070 (CH aromatic), 2990, 2960 (CH alkyl), 2250 (C≡N), 1597, 1562, 1470 (phenyl ring)	7.40 (5H, m, 2H pyridazine and 3H phenyl); 5.50 (1H, s, CH); 4.15 (3H, s, CH_3)
7	3060 (CH aromatic), 2990, 2950 (CH alkyl), 2220 (C≡N), 1600, 1570, 1500 (phenyl ring)	7.35 (5H, m, 2H pyridazine and 3H phenyl); 5.45 (1H, s, CH); 4.20 (3H, s, CH_3)
8	3060 (CH aromatic), 2980, 2840 (CH alkyl), 2260 (C≡N), 1600, 1580, 1500 (phenyl ring)	7.40 (7H, m, 3H pyrimidine and 4H phenyl); 5.20 (1H, s, CH)
9	3060 (CH aromatic), 2960, 2920 (CH alkyl), 2280 (C≡N), 1580, 1500 (phenyl ring)	8.75 (3H, m, pyrimidine); 7.35 (4H, m, phenyl); 5.40 (1H, s, CH)
10	3100 (CH aromatic), 2940 (CH alkyl), 2280 (C≡N), 1580, 1500, 1460 (phenyl ring)	8.20 (6H, m, 3H pyrimidine and 3H phenyl); 6.36 (1H, s, CH)
11	3050 (CH aromatic), 2980, 2940 (CH alkyl), 2260 (C≡N), 1600, 1580, 1540 (phenyl ring)	8.60 (3H, m, pyrimidine); 6.50 (8H, m, phenyl); 5.30 (1H, s, CH); 3.65 (6H, m, $2CH_3$)
12	3060 (CH aromatic), 2980, 2940 (CH alkyl), 2260 (C≡N), 1590, 1530, 1490 (phenyl ring)	8.70 (3H, m, pyrimidine); 6.70 (2H, m, phenyl); 5.35 (1H, s, CH); 3.80 (9H, m, $3CH_3$)
13	3090 (CH aromatic), 2980, 2950 (CH alkyl), 2260 (C≡N), 1580, 1540, 1450 (phenyl ring)	8.60 (3H, m, pyrimidine); 7.65 (7H, m, nahthalene); 5.60 (1H, s, CH)
14	3100 (CH aromatic), 2940, 2860 (CH alkyl), 2220 (C≡N)	8.50 (3H, m, pyrimidine); 7.20 (4H, m, pyridine); 6.70 (1H, s, CH)
15	3090 CH aromatic), 2920, 2860 (CH alkyl), 2250 (C≡N), 1567, 1548, 1495 (phenyl ring)	8.00 (6H, m, 2H pyrimidine and 4H phenyl); 5.20 (1H, s, CH)
16	3100 (CH aromatic), 2920, 2850 (CH alkyl), 2200 (C≡N), 1620, 1570, 1520 (phenyl ring)	7.50 (5H, m, 2H pyrimidine and 3H phenyl); 6.40 (1H, s, CH)
17	3080 (CH aromatic), 2920, 2860 (CH alkyl), 2220 (C≡N), 1610, 1580, 1540 (phenyl ring)	
18	3060 (CH aromatic), 2920, 2850 (CH alkyl), 2190 (C≡N), 1594, 1565, 1520 (phenyl ring)	7.70 (5H, m, 2H pyrimidine and 3H phenyl); 5.20 (1H, s, CH); 3.90 (3H, s, CH_3); 3.65 (3H, s, CH_3)
19	3100 (CH aromatic), 2940, 2840 (CH alkyl), 2200 (C≡N), 1600, 1580, 1530 (phenyl ring)	7.40 (6H, m, 2H pyrimidine and 4H pyridine); 1.65 (1H, s, CH)

TABLE 2 (continued)

1	2	3
20	3100 (CH aromatic), 2980, 2920 (CH alkyl), 2280 (C≡N), 1590, 1530, 1490 (phenyl ring)	8.45 (3H, m, pyrazine); 7.15 (4H, m, phenyl); 5.20 (1H, m, CH)
21	3080 (CH aromatic), 2970, 2930 (CH alkyl), 2260 (C≡N), 1560, 1500, 1440 (phenyl ring)	8.65 (3H, m, pyrazine); 7.40 (4H, m, phenyl); 5.40 (1H, s, CH)
22	3080 (CH aromatic), 2980, 2940 (CH alkyl), 2260 (C≡N), 1590, 1540, 1490 (phenyl ring)	8.60 (3H, m, pyrazine); 7.65 (3H, m, phenyl); 5.75 (1H, s, CH)
23	3080 (CH aromatic), 2980, 2940 (CH alkyl), 2260 (C≡N), 1580, 1540, 1480 (phenyl ring)	6.95(3H, m, pyrazine); 5.95 (3H, m, phenyl); 4.25 (1H, s, CH)
24	3080 (CH aromatic), 2960, 2920 (alkyl), 2260 (C≡N)	6.85 (3H, m, pyrazine); 6.10 (3H, m, phenyl); 5.40 (1H, s, CH)
25	3060 (CH aromatic), 2960, 2920 (CH alkyl), 2260 (C≡N)	6.90 (3H, m, pyrazine); 5.95 (4H, m, phenyl); 4.25 (1H, s, CH); 3.10 (3H, s, CH_3)
26	3080 (CH aromatic), 2960, 2920 (CH alkyl), 2260 (C≡N), 1600, 1530, 1470 (phenyl ring)	8.50 (3H, m, pyrazine); 6.95 (3H, m, phenyl); 5.25 (1H, s, CH); 3.85 (6H, s, $2CH_3$)
27	3080 (CH aromatic), 2960, 2930 (CH alkyl), 2280 (C≡N), 1600, 1580, 1480 (phenyl ring)	8.60 (3H, m, pyrazine); 7.60 (7H, m, nahthalene); 3.90 (1H, s, CH)
28	3080 (CH aromatic), 2960, 2920 (CH alkyl), 2220 (C≡N), 1600, 1540, 1460 (phenyl ring)	8.30 (3H, m, pyrazine); 7.50 (4H, m, pyridine); 5.30 (1H, s, CH)
29	3030 (CH aromatic), 2980, 2960 (CH alkyl), 2260 (C≡N), 1600, 1550, 1490 (phenyl ring)	6.70 (1H, s, pyrazine); 5.90 (3H, m, phenyl); 4.30 (1H, s, CH); 2.10 (6H, m, $2CH_3$)
30	3030 (CH aromatic), 2980, 2940 (CH alkyl), 2220 (C≡N), 1620, 1580, 1530 (phenyl ring)	6.60 (1H, s, pyrazine); 5.85 (3H, m, phenyl); 4.90 (1H, s, CH); 2.10 (6H, m, $2CH_3$)
31	3060 (CH aromatic), 2930, 2830 (CH alkyl), 2250 (C≡N), 1595, 1560, 1480 (phenyl ring)	6.90 (4H, m, 1H pyrazine and 3H phenyl); 5.40 (1H, s, CH); 3.90 (6H, s, $2CH_3$); 2.60 (6H, s, $2CH_3$)

***** Compounds **1-9**, **11-13**, **15**, **18-27**, **29-31** in $CDCl_3$, compounds **10**, **14**, **16**, **28** – in DMSO-d_6.

Scheme 2



1–31

The foregoing syntheses gave 31 new compounds: 2-cyanomethylpyridazine derivatives **1-7**, 2-cyanomethylpyrimidine derivatives **8-19**, and 2-cyanomethylpyrazine derivatives **20-31**. Their structures were established by the analyses of IR and ^1H NMR spectra. Spectral data, physical properties of the compounds obtained, and reactions yields are given in Table 1.

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 Varian Gemini 200 apparatus at (200 MHz) with TMS as an internal standard.

Reactions of Chlorodiazines with Arylacetonitriles 1-31 (General Method). To 4-chlorophenylacetonitrile (1.5 g, 10 mmol) in DMSO (2.5 ml) 2-chloropyrazine (1.1 g, 10 mmol) and 50% aqueous NaOH (1.5 ml) were added. The whole was heated at 70°C for 3 h with vigorous stirring. On cooling the reaction mixture was treated with water (30 ml) and acidified with concentrated HCl to pH 3. The resulted precipitate was crystallized from 50% aqueous ethanol. Compound **21** was obtained (1.1 g, yield 48%; mp 103-107°C).

R E F E R E N C E S

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