Studies on Pyrazines. 24 [1]. A Simple and Versatile Synthetic Method for 3-Alkoxy- and 3-Aminopyrazinecarbonitriles

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New and concise synthetic methods of 3-alkoxy- and 3-aminopyrazinecarbonitriles by nucleophilic displacement of 3-phenylsulfonylpyrazinecarbonitriles are reported.

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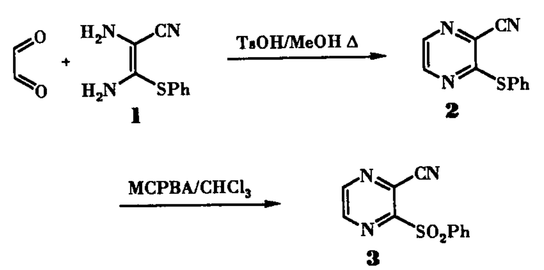
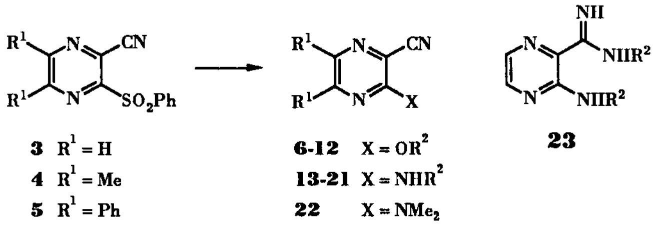
Recently, 2,3-diamino-3-phenylthioacrylonitrile (**1**), an adduct of thiophenol to the trimer of hydrogen cyanide, was found to be directly prepared by the reaction of hydrogen cyanide with phenyl disulfide in the presence of base [2]. This novel diamine **1** undergoes condensation with α-diketones yielding 3-phenylthiopyrazinecarbonitrile (**2**) and a variety of its alkyl and aryl analogues. The sulfide function of **2** is easilyl oxidized with *m*-chloroperbenzoic acid (MCPBA) under mild conditions to produce 3-phenylsulfonylpyrazinecarbonitrile (**3**) [2]. Bearing an efficient-leaving phenylsulfonyl group [3,4] adjacent to an electron-withdrawing cyano substituent, the sulfone **3** is of great interest as a versatile intermediate for synthesis of other 3-substituted pyrazinecarbonitriles. Indeed, Grignard reaction of **3** was shown to give a series of 3-alkyl- and 3-arylpyrazinecarbonitriles by replacement of the phenylsulfonyl group [5]. In this paper, we show additional examples of the successful nucleophilic displacement of sulfone **3**, alkoxylation and amination, which are applicable for the 5,6-dimethyl **4** and 5,6-diphenyl substituted ones **5** as well as for a wide spectrum of alkoxides and amines. Those alkoxy and amino pyrazinecarbonitriles are attracting attention as synthetic intermediates for chemotherapeutically useful pyrazinecarboxamide derivatives [6].

Scheme 1



Treatment of the sulfone **3** with methanolic sodium methoxide at room temperature gave an 81% yield of methoxypyrazine **6**. As expected, this alkoxylation proceeded much faster than that of the pyrazinyl sulfone itself as 2-methylsulfonylpyrazine [3], and the cyano sulfonyl compound **3** was completely consumed within 30 minutes. However with the base-catalyzed alkoxylation of 2,3-pyrazinedicarbonitrile [7], the present procedure enabled a remarkable reduction of the reaction time and considerable improvement of yields. The product **6** had also been prepared from 3-chloropyrazinecarbonitrile [8] by treatment with the same reagents in a better yield, but the route from **3** was advantageous in view of the accessibility of the starting material. The sulfone **3** underwent similar alkoxylation with various alcohols to give the corresponding 3-alkoxypyrazinecarbonitriles **6-10**, yields of which were reflected by the bulkiness of nucleophiles. The use of tetrahydrofuran (THF) instead of alcohol as the solvent mostly suppressed the alkoxylation. Displacement of **5** with potassium 4-butoxyphenoxide, however, was executed in THF to afford **12** in 78% yield. Another oxygen nucleophile which was examined, acetate anion, did not lead to 3-acetoxypyrazinecarbonitrile although the starting material **3** was entirely consumed in refluxing acetonitrile containing crown ether for 1 hour.

Scheme 2



As can be seen, the cyano substituent facilitates displacement of the neighboring sulfonyl group with alkoxide, whose effect is more explicitly exhibited by the following amination reactions. Thus, although conversion of 2-methylsulfonylpyrazine to the 2-propylamino compound required harsh reaction conditions at 150° for 15 hours [4], the cyano sulfone **3** underwent amination at room temperature by treating with aqueous ammonium hydroxide and triethylamine in THF to furnish 3-aminopyrazinecarbonitrile (**13**) in 82% yield after 6 hours. Similar treatment of 2,3-pyrazinedicarbonitrile gave only a 5% of **13** [9]. Since this product **13** is a useful building block for synthesis of pteridine compounds, some of synthetic methods proposed previously [9,10], but the present procedure appears to be the best method of choice for synthesis of **13** in terms of simplicity and availability of the starting material. Aminopyrazines **14** and **15** were more easily obtained by treatment of **3** with aqueous methylamine and ethylamine, respectively. On the other hand, amination with isopropylamine and benzylamine required a longer reaction period resulting in the formation of by-product, *N*-alkylamidine **23**, which were formed by addition of the amines in excess to the desired products, **16** and **17**. Fortunately these by-products could be removed by recrystallization. Diphenyl substituted pyrazinecarbonitrile **5** is more reactive than the parent sulfone **3** to undergo amination with even 4-methylaniline and dimethylamine yielding **21** and **22**, respectively.

Table 1

Preparation of Alkoxy- and Aminopyrazinecarbonitriles

Compound	R^1	X	Time (hours)	Yield (%)
6	H	MeO	1	81
7	H	EtO	1	75
8	H	*i*-PrO	1	68
9	H	*s*-BuO	1	42
10	H	*t*-BuO	2	53
11	Ph	MeO	24	80
12	Ph	4-BuO-C_6H_4O	3	78
13	H	NH_2	6	82
14	H	MeNH	1	84
15	H	EtNH	2	78
16	H	*i*-PrNH	24	63
17	H	BuNH	24	70
18	Me	MeNH	8	64
19	Ph	NH_2	24	83
20	Ph	MeNH	1	86
21	Ph	4-Me-C_6H_4NH	40	34
22	Ph	Me_2N	0.1	85

In either substitution, mild reaction conditions prevent the labile cyano group from an addition reaction with the nucleophiles resulting in the formation of imidates or amidines as above. To this end, we attempted to convert phenylthiopyrazine **2** into the above alkoxy and aminopyrazines, but most of the starting material **2** was recovered.

EXPERIMENTAL

All melting points were determined using a Büchi 535 apparatus and are uncorrected. Boiling points are uncorrected. The ir spectra were recorded on a JASCO IR-810 or a Perkin Elmer FT-IR 1760-X spectrometer. The nmr spectra were obtained with a JEOL JNM EX270 or GSX-400 instrument in a solution of deuteriochloroform containing tetramethylsilane as the internal standard.

3-Phenylthiopyrazinecarbonitrile (**2**).

This compound was prepared according to the procedure in the literature [2]. A solution of **1** (19.25 g, 0.10 mole), 40% glyoxal (15.0 g, 0.10 mole) and *p*-toluenesulfonic acid monohydrate (19.1 g, 0.10 mole) in methanol (150 ml) was refluxed with stirring for 5 hours. After cooling to room temperature, a light tan precipitate was produced, part of which had formed already during heating, and was collected by filtration and washed with a small amount of methanol. The filtrate and washings were condensed to about 75 ml and refrigerated overnight to give the second crop (total yield, 16.48 g, 77%). The combined products were recrystallized from methanol (300 ml) affording golden prisms (14.81 g, 69%), mp 130-131°, lit [2] mp 134-135.5°; ir (potassium bromide): 2230, 1503, 1355, 1190, 1160, 1080, 750 cm^{-1}; ^{1}H nmr: δ 7.26-7.50 (m, 3H), 7.56-7.60 (m, 2H), 8.34 (d, J = 2.3 Hz, 1H), 8.41 (d, 1H); ^{13}C nmr: δ 114.3, 126.5, 127.5, 129.7, 130.2, 135.7, 140.5, 146.3, 161.4.

3-Phenylsulfonylpyrazinecarbonitrile (**3**).

This compound was also prepared in accordance with the literature [2]. MCPBA (minimum contained 70%, 27.7 g) was added in small portions to a stirred solution of **2** (13.87 g, 65 mmoles) in chloroform (280 ml) below 10°. The mixture was stirred at room temperature for 3 hours. The insoluble material formed was removed by filtration, and the filtrate was washed with aqueous sodium carbonate and then water. After drying over magnesium sulfate, the solution was evaporated, and the residue was recrystallized from ethanol (250 ml) to give colorless prisms (14.46 g, 91%), mp 126-127°, lit [2] mp 120.5-121.5°; ir (potassium bromide): 2250, 1445, 1382, 1330, 1155, 1075, 607 cm^{-1}; ^{1}H nmr: δ 7.40-7.60 (m, 3H), 8.15-8.19 (m, 2H), 8.82 (d, J = 2.3 Hz, 1H), 8.87 (d, 1H); ^{13}C nmr: δ 113.1, 128.4, 129.7 (2C), 135.3, 137.0, 146.0, 147.1, 157.1.

In the same fashion, the sulfones **4** and **5** were prepared.

General Procedure for 2-Alkoxypyrazinecarbonitriles **6-10**.

The sulfone **3** (0.245 g, 1.0 mmole) was added to alcoholic sodium alkoxide, which was prepared from sodium (27 mg, 1.2 mmoles) and dry alcohol (7.0 ml) by heating if necessary, and the mixture was stirred at room temperature for the time given in Table 1. The starting material was shown by tlc to be almost consumed within 30 minutes. After evaporation *in vacuo*, the residue was chromatographed on silica gel (5 g) eluted with hexane/ethyl acetate (6:1) affording the following compounds.

3-Methoxypyrazinecarbonitrile (**6**).

This compound was obtained as colorless needles (hexane), mp 55°, lit [6] mp 55°; ir (potassium bromide): 2240, 1535, 1395, 1175, 1145, 870 cm^{-1}; ^{1}H nmr: δ 4.12 (s, 3H), 8.29 (d, J = 2.6 Hz, 1H), 8.50 (d, 1H); ^{13}C nmr: δ 54.9, 114.0, 119.7, 137.5, 144.6, 161.7.

3-Ethoxypyrazinecarbonitrile (**7**).

This compound was obtained as colorless needles (hexane), mp 43°, lit [7] mp 43-44°; ir (potassium bromide): 2240, 1535, 1425, 1145, 1020, 870 cm^{-1}; ^{1}H nmr: δ 1.48 (t, J = 6.9 Hz, 3H), 4.54 (q, 2H), 8.25 (d, J = 2.6 Hz, 1H), 8.32 (d, 1H); ^{13}C nmr: δ 14.2, 64.1, 114.1, 119.7, 137.2, 144.6, 161.4.

3-(2-Propyloxy)pyrazinecarbonitrile (**8**).

This compound was obtained as colorless prisms (hexane), mp 52-53°; ir (potassium bromide): 2990, 2240, 1525, 1418, 1320, 930 cm^{-1}; ^{1}H nmr: δ 1.43 (d, J = 6.3 Hz, 6H), 5.41 (septet, 1H), 8.22 (d, J = 2.6 Hz, 1H), 8.30 (d, 1H); ^{13}C nmr: δ 21.7, 71.8, 114.2, 119.9, 136.9, 144.5, 161.2.

Anal. Calcd. for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 58.86; H, 5.62; N, 25.83.

3-(2-Butyloxy)pyrazinecarbonitrile (**9**).

This compound was obtained as an oil, bp 85°/3 mm Hg (Kugelrohr); ir (neat): 2970, 2240, 1525, 1418, 1180, 1140, 925, 860 cm^{-1}; ^{1}H nmr: δ 1.00 (t, J = 7.6 Hz, 3H), 1.39 (d, J = 6.3 Hz, 3H), 1.82 (d of q, 2H), 5.25 (sextet, 1H), 8.23 (d, J = 2.6 Hz, 1H), 8.31 (d, 1H); ^{13}C nmr: δ 9.6, 19.1, 28.7, 60.4, 114.2, 119.8, 136.9, 144.6, 161.5.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.75; H, 6.09; N, 23.81.

3-(2-Methyl-2-propyloxy)pyrazinecarbonitrile (**10**).

This compound was obtained by treatment with commercially available potassium *tert*-butoxide in *tert*-butyl alcohol, bp 80°/3 mmHg (Kugelrohr); ir (neat): 2990, 2240, 1525, 1405, 1180, 930, 835 cm^{-1}; ^{1}H nmr: δ 1.66 (s, 9H), 8.20 (d, J = 2.6 Hz, 1H), 8.28 (d, 1H); ^{13}C nmr: δ 28.2, 60.4, 114.5, 120.9, 136.6, 143.9, 161.5.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.89; H, 5.96; N, 24.05.

5,6-Diphenyl-3-methoxypyrazinecarbonitrile (**11**).

This compound was prepared in the same manner by using **5** instead of **3**, mp 168-169°, lit [7] mp 165-167°; ir (potassium bromide): 2230, 1540, 1463, 1387, 1333, 1197, 1178, 700 cm^{-1}; ^{1}H nmr: δ 4.18 (s, 3H), 7.23-7.35 (m, 10H); ^{13}C nmr: δ 54.7, 114.4, 115.6, 128.2, 128.3, 128.7, 129.4, 129.9, 136.8, 136.9, 146.2, 152.6, 159.3.

3-(4-Butoxyphenoxy)-5,6-diphenylpyrazinecarbonitrile (**12**).

4-Butoxyphenol (1.0 g, 2.0 mmoles) was dissolved in a solution in methanol (10 ml) containing potassium hydroxide (0.4 g, 7 mmoles) and then the mixture was evaporated *in vacuo*. The residue was dissolved in tetrahydrofuran (20 ml) and sulfone **5** (0.80 g, 2.0 mmoles) was added to it. The resulting mixture was stirred at room temperature for 3 hours, and worked up as described above to give **12** (0.66 g, 78%), mp 153-154° (ethanol); ir (potassium bromide): 2940, 2230, 1539, 1505, 1410, 1388, 1203, 700 cm^{-1}; ^{1}H nmr: δ 1.00 (t, 3H), 1.52 (m, 2H), 1.78 (m, 2H), 3.98 (t, 2H), 6.94 (d, 2H), 7.14-7.46 (m, 12H); ^{13}C nmr: δ 13.8, 18.2, 31.3, 68.1, 114.3, 115.1, 115.7, 122.2, 128.2, 128.4, 128.9, 129.4, 129.9, 136.2, 136.9, 145.3, 147.6, 152.6, 156.8, 158.9.

Anal. Calcd. for $C_{27}H_{23}N_3O_2$: C, 76.94; H, 5.50; N, 9.97. Found: C, 77.05; H, 5.74; N, 9.89.

General Procedure for 3-Aminopyrazinecarbonitriles **13-22**.

An amine (3.0 mmoles) was added to a solution of **3**, **4** or **5** (1.0 mmole) in tetrahydrofuran (10 ml) containing triethylamine (0.56 ml, 4.0 mmoles) and water (0.35 ml) when free amine was used, and the mixture was stirred at room temperature for the period given in Table 1. For synthesis of **13**, the same quantity of 25% ammonium hydroxide was added to the reaction mixture at the halfway point. After evaporation *in vacuo* to dryness, the residue was subjected to chromatography on silica gel (5 g) eluted with hexane-ethyl acetate (1:1). The resulting eluate was evaporated *in vacuo* and recrystallized to yield the following 3-aminopyrazinecarbonitriles.

3-Aminopyrazinecarbonitrile (**13**).

This compound was obtained as pale yellow needles (water), mp 193-194°, lit [9] mp 192°; ir (potassium bromide): 3400, 2220, 1660, 1197, 840 cm^{-1}; ^{1}H nmr: δ 5.26 (br s, 2H), 8.03 (d, J = 2.2 Hz, 1H), 8.22 (d, 1H); ^{13}C nmr: δ 114.0, 119.7, 137.5, 144.6, 161.7.

3-Methylaminopyrazinecarbonitrile (**14**).

The compound was obtained as pale yellow needles (methanol), mp 149-150°, lit [11] mp 142-143°; ir (potassium bromide): 3370, 2220, 1590, 1202, 845 cm^{-1}; ^{1}H nmr: δ 3.08 (s, 1.5H), 3.09 (s, 1.5H), 5.43 (br s, 1H), 7.89 (d, J = 2.6 Hz, 1H), 8.24 (d, 1H); ^{13}C nmr: δ 28.0, 114.5, 115.3, 133.2, 146.2, 156.3.

3-Ethylaminopyrazinecarbonitrile (**15**).

This compound was obtained as pale yellow needles (2-propanol), mp 99-100°; ir (potassium bromide): 3360, 2220, 1585, 1195, 858 cm^{-1}; ^{1}H nmr: δ 1.29 (t, J = 7.3 Hz, 3H), 3.53 (q, 1.5H), 3.56 (q, 1.5H), 5.33 (br s, 1H), 7.88 (d, J = 2.6 Hz, 1H), 8.22 (d, 1H); ^{13}C nmr: δ 14.6, 36.2, 114.3, 115.3, 133.2, 146.2, 155.7.

Anal. Calcd. for $C_7H_8N_4$: C, 56.74; H, 5.44; N, 37.81. Found: C, 57.02; H, 5.44; N, 37.52.

3-(2-Propylamino)pyrazinecarbonitrile (**16**).

This compound was obtained as colorless prisms (hexane), mp 64-64.5°; bp 105°/3 mmHg (Kugelrohr); ir (potassium bromide): 3360, 2210, 1580, 1510, 1195, 850 cm^{-1}; ^{1}H nmr: δ 1.29 (d, J = 6.6 Hz, 6H), 4.30 (septet, 1H), 5.07 (br s, 1H), 7.86 (d, J = 2.3 Hz, 1H), 8.21 (d, 1H); ^{13}C nmr: δ 22.6, 43.1, 114.2, 115.3, 133.1, 146.2, 155.1.

Anal. Calcd. for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.49; H, 6.22; N, 34.36.

3-Benzylaminopyrazinecarbonitrile (**17**).

This compound was obtained as pale yellow plates (hexane), mp 102-103°; ir (potassium bromide): 3340, 3360, 2230, 1590, 1575, 1200, 860 cm^{-1}; ^{1}H nmr: δ 4.69 (s, 1H), 4.71 (s, 1H), 5.63 (br s, 1H), 7.24-7.41 (m, 5H), 7.93 (d, J = 2.3 Hz, 1H), 8.24 (d, 1H); ^{13}C nmr: δ 45.1, 114.4, 115.2, 127.8, 127.9, 128.9, 133.8, 137.5, 146.1, 155.5.

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.67; H, 5.02; N, 26.37.

5,6-Dimethyl-3-methylaminopyrazinecarbonitrile (**18**).

This compound was prepared by using sulfone **4** instead of **3** in the same manner as described above, mp 174-175° (ethanol); ir (potassium bromide): 3380, 2930, 2220, 1587, 1500, 1231 cm^{-1}; ^{1}H nmr: δ 2.38 (s, 3H), 2.46 (s, 3H), 3.05 (d, 3H), 5.10 (br s, 1H); ^{13}C nmr: δ 20.5, 22.6, 27.9, 109.3, 116.2, 140.7, 154.8, 155.5.

Anal. Calcd. for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.44; H, 6.25; N, 34.33.

The following compounds were prepared in the same manner by using **5** instead of **3**.

3-Amino-5,6-diphenylpyrazinecarbonitrile (**19**).

This compound had mp 172-173° (ethanol), lit [12] mp 160-163°; ir (potassium bromide): 3360, 3190, 2240, 1650, 1548, 1462, 1447, 1399 cm^{-1}; ^{1}H nmr: δ 5.35 (br s, 2H), 7.23-7.43 (m, 10H); ^{13}C nmr: δ 110.6, 115.5, 128.23, 128.28, 128.33, 129.3, 129.6, 129.7, 137.3, 144.4, 154.0, 154.5.

5,6-Diphenyl-3-methylaminopyrazinecarbonitrile (**20**).

This compound had mp 170-171° (ethanol); ir (potassium bromide) 3350, 3060, 2230, 1590, 1538, 1486, 1434, 1407, 1368, 1203, 700 cm^{-1}; ^{1}H nmr: δ 3.17 (d, 3H), 5.36 (br s, 1H), 7.22-7.50 (m, 10H); ^{13}C nmr: δ 28.0, 110.9, 115.8, 128.0, 128.1, 128.2, 129.3, 129.5, 129.9, 137.8, 137.9, 142.1, 153.8, 154.1.

Anal. Calcd. for $C_{18}H_{14}N_4$: C, 75.51; H, 4.93; N, 19.57. Found: C, 75.63; H, 5.12; N, 19.73.

5,6-Diphenyl-3-(4-tolylamino)pyrazinecarbonitrile (**21**).

This compound was obtained using DBU instead of triethylamine. The reaction could not be completed by stirring at room temperature for 40 hours, mp 215-216° (ethanol); ir (potassium bromide): 3340, 2230, 1607, 1562, 1538, 1510, 1480, 1429, 1408, 1371, 1196 cm^{-1}; ^{1}H nmr: δ 2.35 (s, 3H), 7.1-7.6 (m, 15H); ^{13}C nmr: δ 20.9, 111.8, 115.4, 120.6, 128.2, 128.3, 128.4, 129.3, 129.6, 129.7, 129.9, 133.9, 135.3, 137.4, 144.0, 151.0, 153.4.

Anal. Calcd. for $C_{24}H_{18}N_4$: C, 79.54; H, 5.01; N, 15.46. Found: C, 79.62; H, 5.28; N, 15.51.

3-Dimethylamino-5,6-diphenylpyrazinecarbonitrile (**22**).

This compound had mp 140-140.5° (ethanol); ir (potassium bromide): 2220, 1563, 1410, 1384, 1223, 698 cm^{-1}; ^{1}H nmr: δ 3.40 (s, 6H), 7.22-7.53 (m, 10H); ^{13}C nmr: δ 39.6, 107.6, 118.2, 128.0, 128.1, 128.2, 129.1, 129.4, 129.8, 137.3, 137.6, 142.1, 151.9, 153.3.

Anal. Calcd. for $C_{19}H_{16}N_4$: C, 75.98; H, 5.37; N, 18.65. Found: C, 76.12; H, 5.54; N, 18.67.

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