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β-ELIMINATION OF THE PYRAZINYLSULFINYL GROUP — PREPARATION OF CINNAMONITRILES

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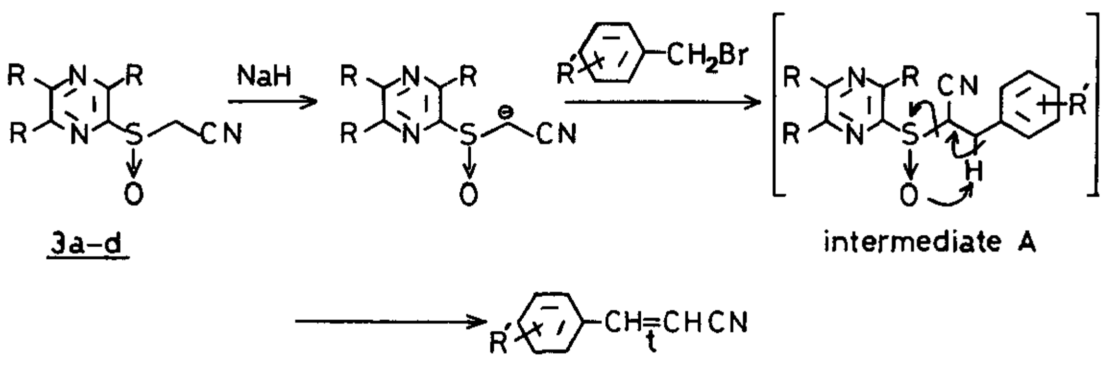
Abstract — As a new leaving group for the β-elimination of sulfoxides, the pyrazinylsulfinyl group was introduced. Using this leaving group, some cinnamonitriles were prepared from the corresponding benzyl bromides and chloroacetonitrile.

The β-elimination of sulfoxides as first noted by Cram et al.[1] is very useful for introducing a double bond into certain structures.[2] Although in this reaction, the phenylsulfinyl group is generally used as the leaving group, the reaction is often time-consuming. Further, thiophenol, the starting material for the phenylsulfinyl group, has a bad smell. Thus, to avoid these problems, the pyrazinylsulfinyl group was examined for use as a leaving group in this elimination reaction. The desired pyrazinyl sulfoxides were derived from the

Scheme 1

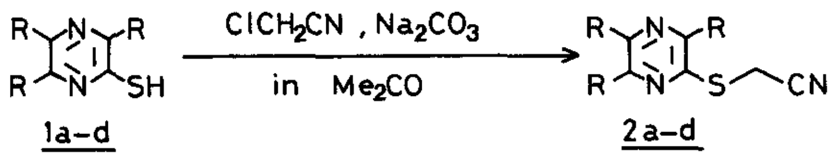


3a-d

corresponding thiols, as evident from Tables 1 and 2. 3,6-Dialkyl-2-pyrazinethiols (1a-c) could easily be prepared from appropriate commercial amino acids *via* 3,6-dialkyl-2-hydroxypyrazines[3]. 5,6-Diphenyl-2-pyrazinethiol (1d) was prepared from 5,6-diphenyl-2-hydroxypyrazine[4] using Lawesson's reagent[5] under essentially the same conditions as for the syntheses of 1a-c. These thiols have no offensive smell and can be handled easily. In this report, the preparation of cinnamonitriles from the corresponding benzyl bromides and chloroacetonitrile using this sulfinyl group is presented.

The preparation of 2-cyanomethylthiopyrazines (2a-d) was carried out according to the method of Nokami *et al.*[6]. As shown in Table 1, all products were obtained

Table 1. Physical Properties of 2-Cyanomethylthiopyrazines (2a-d)



3,6-Diethyl-2-cyanomethylthiopyrazine (2a): mp 45-46°C; yield 99%; ms: m/z 207 (M^+); ir (KBr): 2220 cm^{-1}(ν_{CN}); ^{1}H-nmr ($CDCl_3$/TMS): δ 1.25 (t, J = 5 Hz, 3H, CH_2CH_3), 1.30 (t, J = 5 Hz, 3H, CH_2CH_3), 2.71 (q, J = 7 Hz, 2H, CH_2CH_3), 2.79 (q, J = 7 Hz, 2H, CH_2CH_3), 3.93 (s, 2H, CH_2CN), 8.15 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{10}H_{13}N_3S$: C, 57.94; H, 6.32; N, 20.27. Found: C, 58.18; H, 6.36; N, 20.27.

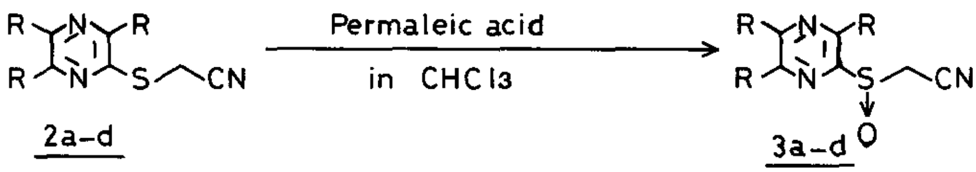
3,6-Diisopropyl-2-cyanomethylthiopyrazine (2b): mp 79-80°C; yield 95%; ms: m/z 235 (M^+); ir (KBr): 2220 cm^{-1}(ν_{CN}); ^{1}H-nmr ($CDCl_3$/TMS): δ 1.26 (d, J = 4 Hz, 6H, $CH(CH_3)_2$), 1.31 (d, J = 4 Hz, 6H, $CH(CH_3)_2$), 2.90-3.20 (m, 2H, 2 x $CH(CH_3)_2$), 3.90 (s, 2H, CH_2CN), 8.13 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{12}H_{17}N_3S$: C, 61.24; H, 7.28; N, 17.85. Found: C, 61.15; H, 7.29; N, 17.80.

3,6-Diisobutyl-2-cyanomethylthiopyrazine (2c): bp 175-180°C/6 torr; yield 96%; ms: m/z 264 (M^+); ir (neat): 2220 cm^{-1}(ν_{CN}); ^{1}H-nmr ($CDCl_3$/TMS): δ 0.94 (d, J = 6 Hz, 12H, 2 x $CH_2CH(CH_3)_2$), 1.56-2.30 (m, 2H, 2 x $CH_2CH(CH_3)_2$), 2.56 (d, J = 7 Hz, 4H, 2 x $CH_2CH(CH_3)_2$), 3.90 (s, 2H, CH_2CN), 8.03 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{14}H_{21}N_3S$: C, 63.85; H, 8.04; N, 15.96. Found: C, 63.91; H, 8.16; N, 16.02.

5,6-Diphenyl-2-cyanomethylthiopyrazine (2d): mp 103-105°C; yield 95%; ms: m/z 303 (M^+); ir (KBr): 2250 cm^{-1}(ν_{CN}); ^{1}H-nmr ($CDCl_3$/TMS): δ 3.80 (s, 2H, CH_2CN), 7.00-7.26 (m, 10H, benzene H), 8.23 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{18}H_{13}N_3S$: C, 71.26; H, 4.39; N, 13.92. Found: C, 71.46; H, 4.38; N, 13.84.

in almost quantitative yields. They were oxidized with permaleic acid (PMA) prepared from maleic anhydride and 90% hydrogen peroxide to give the corresponding sulfoxides (3a-d). As shown in Table 2, compounds 3a, 3b and 3d were obtained in good yields. However, under the same conditions, 2c gave many products which could hardly be separated. Compound 3c was obtained in 42% yield using 5 times the solvent volume as that for the other sulfoxides. These sulfoxides (3a-d) were metalated with sodium hydride in 1,2-dimethoxyethane

Table 2. Physical Properties of 2-Cyanomethylsulfinylpyrazines (3a-d)



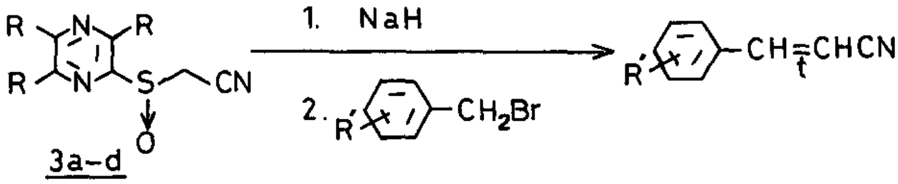
3,6-Diethyl-2-cyanomethylsulfinylpyrazine (3a): bp 105-110°C/4 torr; yield 81%; ms: m/z 223 (M^+), 135 (M^+-$SOCH_2CN$); ir (neat): 1060 (ν_{SO}), 2250 (ν_{CN}) cm^{-1}; ^{1}H-nmr ($CDCl_3$/TMS): δ 1.36 (t, J = 8 Hz, 6H, 2 x $CH_2C\underline{H}_3$), 2.94 (q, J = 7 Hz, 2H, $C\underline{H}_2CH_3$), 3.18 (q, J = 7 Hz, 2H, $C\underline{H}_2CH_3$), 3.99 (d, J = 15 Hz, 1H, $SOC\underline{H}_aCN$), 4.40 (d, J = 15 Hz, 1H, $SOC\underline{H}_bCN$), 8.60 (s, 1H, pyrazine H) ppm; High resolution mass: Calcd. for $C_{10}H_{13}N_2OS$: 223.0781. Found: 223.0794.

3,6-Diisopropyl-2-cyanomethylsulfinylpyrazine (3b): bp 130-140°C/8.5 torr; yield 78%; ms: m/z 252 (M^+), 163 (M^+-$SOCH_2CN$); ir (neat): 1050 (ν_{SO}), 2250 (ν_{CN}) cm^{-1}; ^{1}H-nmr ($CDCl_3$/TMS): δ 1.37 (d, J = 7 Hz, 12H, 2 x $CH(C\underline{H}_3)_2$), 2.93-3.30 (m, 1H, $C\underline{H}(CH_3)_2$), 3.40-3.70 (m, 1H, $C\underline{H}(CH_3)_2$), 3.96 (d, J = 15 Hz, 1H, $SOC\underline{H}_aCN$), 4.43 (d, J = 15 Hz, 1H, $SOC\underline{H}_bCN$), 8.56 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{12}H_{17}N_3SO$: C, 57.34; H, 6.82; N, 16.72. Found: C, 57,52; H, 6.97; N, 16.79.

3,6-Diisobutyl-2-cyanomethylsulfinylpyrazine (3c): bp 90-100°C/4 torr; yield 42%; ms: m/z 279 (M^+), 191 (M^+-$SOCH_2CN$); ir (neat): 1063 (ν_{SO}), 2250 (ν_{CN}) cm^{-1}; ^{1}H-nmr ($CDCl_3$/TMS): δ 0.93 (d, J = 6 Hz, 12H, 2 x $CH_2CH(C\underline{H}_3)_2$), 1.66-2.30 (m, 2H, 2 x $CH_2C\underline{H}(CH_3)_2$), 2.68 (d, J = 7 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 2.90 (d, J = 6 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 3.86 (d, J = 14 Hz, 1H, $SOC\underline{H}_aCN$), 4.27 (d, J = 15 Hz, 1H, $SOC\underline{H}_bCN$), 8.30 (s, 1H, pyrazine H) ppm; High resolution mass: Calcd. for $C_{14}H_{21}N_3OS$: 279.1407. Found: 279.1439.

5,6-Diphenyl-2-cyanomethylsulfinylpyrazine (3d): mp 92-95°C; yield 81%; ms: m/z 319 (M^+), 231 (M^+-$SOCH_2CN$); ir (KBr): 1065 (ν_{SO}), 2220 (ν_{CN}) cm^{-1}; ^{1}H-nmr ($CDCl_3$/TMS): δ 3.98 (d, J = 12 Hz, 1H, $SOC\underline{H}_aCN$), 4.06 (d, J = 12 Hz, 1H, $SOC\underline{H}_bCN$), 7.23-7.40 (m, 10H, benzene H), 9.13 (s, 1H, pyrazine H) ppm; High resolution mass: Calcd. for $C_{18}H_{13}N_3OS$: 319.0781. Found: 319.0758.

Table 3. Preparation of Cinnamonitriles



Entry	R'	2-Cyanomethyl-sulfinylpyrazines	Products	Yield (%)	mp (°C) or bp (°C/torr)
1	p-Me	3a	p-Methylcinnamo-nitrile	56	79-81 (79-80)[7]
2	p-Br	3a	p-Bromocinnamo-nitrile	35	104-106 (106.5-107.0)[8]
3	H	3b	Cinnamonitrile	67	65-80/5 (129/12)[9]
4	o-Me	3b	o-Methylcinnamo-nitrile	52	70-80/5 (147-150/24)[7]
5	m-Me	3b	m-Methylcinnamo-nitrile	39	60-68/4 (45/14)[9]
6	p-Me	3b	p-Methylcinnamo-nitrile	64	79-81 (79-80)[7]
7	p-Br	3b	p-Bromocinnamo-nitrile	49	104-106 (106.5-107.0)[8]
8	p-Me	3c	p-Methylcinnamo-nitrile	39	79-81 (79-80)[7]
9	p-Br	3c	p-Bromocinnamo-nitrile	58	104-106 (106.5-107.0)[8]
10	p-Me	3d	p-Methylcinnamo-nitrile	12	79-81 (79-80)[7]

(DME) and various benzyl bromides were added to the carbanion solution. When the mixture was refluxed, the reaction shown in Table 3 took place within 15 min to give the corresponding trans-cinnamonitriles. An intermediate **A** in this reaction depicted in Scheme 1 may possibly have been formed on the basis of data from an experiment, in which an adequate quantity of sodium hydride was examined. Namely, compound **3b** was treated with various quantities of sodium hydride (1.0, 1.5, and 2.0 eq.) and 1.0 eq. of benzyl bromide successively. Cinnamonitrile was obtained in 62, 67, and 51% yields, respectively. These results indicate that 2.0 eq. of sodium hydride had essentially the same effect as 1.0 eq. The authors consider that the pulling out of an α-proton from the benzyl group occurred through the action of an oxygen atom of sulfoxide. Next, an attempt was made to isolate an intermediate **A** to confirm its structure, but without success even though the reaction was conducted at lower temperature. As can be seen from Table 3, compound **3d** is obviously inferior to the other sulfoxides for this reaction. This compound gave the corresponding cinnamonitrile in low yield and also its preparation was more difficult compared to the others. Under the same conditions, the preparation of p-methylcinnamonitrile using cyanomethylsulfinylbenzene[6] instead of **3b** was examined. However, the desired product could not be obtained.

From these results, the pyrazinylsulfinyl group is considered a superior leaving group for β-elimination of sulfoxides for the following two reasons:

1. The elimination rate is much faster than when using the phenylsulfinyl group. (within a period of 15 min.)
2. Pyrazinethiols do not have the characteristic bad odor of mercaptans.

EXPERIMENTAL

None of the melting or boiling points were corrected. The following instruments were used to obtain spectral data. ^{1}H-Nmr: Varian EM-360 and EM-390; Ir spectra: Shimadzu IR-400; Ms: Hitachi M-80 spectrometer.

Preparation of 5,6-Diphenyl-2-pyrazinethiol (1d)

A mixture of 5,6-diphenyl-2-hydroxypyrazine[4] (496 mg; 2 mmol) and Lawesson's reagent[5] (404 mg; 1 mmol) was refluxed for 3.5 h in benzene (50 ml). After cooling, the reaction mixture was acidified to pH 4.7 with AcOH and the yellow precipitates were collected by filtration. The filtrate was extracted with benzene and the extract was dried over Na_2SO_4. The solvent was evaporated to give a yellow solid. Both compounds were combined and recrystallized from EtOH to give 5,6-diphenyl-2-pyrazinethiol as yellow needles (514 mg, 97%).
5,6-Diphenyl-2-pyrazinethiol (1d): mp 176-181°C; yield 97%; ms: m/z 264 (M^+); ^{1}H-nmr (DMSO-d_6/TMS): δ 7.10 (d, J = 9 Hz, 10H, benzene H), 8.45 (s, 1H, pyrazine H) ppm; Anal. Calcd. for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.60. Found: C, 72.89; H, 4.62; N, 10.62.

General Procedure for Preparation of 2-Cyanomethylthiopyrazines (2a-d)

A solution of chloroacetonitrile (1.2 eq.) previously dissolved in Me_2CO (2 ml) was added dropwise over a 10 min period to a suspension of a 2-pyrazinethiol (1a-d) and Na_2CO_3 in Me_2CO (20 ml) at 60°C with stirring. After stirring for 5 h, the reaction mixture was filtered and the filtrate concentrated *in vacuo* to give a yellow solid. By recrystallization from hexane, a pure 2-cyanomethylthiopyrazine (2a-d) was obtained as colorless needles.

General Procedure for Preparation of 2-Cyanomethylsulfinylpyrazines (3a-d)

A solution of a 2-cyanomethylthiopyrazine (2a-d) (1 mmol), 90% hydrogen peroxide (1.2 mmol) and maleic anhydride (1.2 mmol) in $CHCl_3$ (10 ml) was allowed to stand overnight. The reaction mixture was refluxed for 2 h and then washed with H_2O, 10% $KHCO_3$ and H_2O successively. The $CHCl_3$ layer was dried over Na_2SO_4 and the solvent was evaporated off *in vacuo*. The residual solid was applied onto a silica gel colomun (Wakogel C-200, 30g). Elution with a mixture of hexane-ethyl acetate (7:3) gave a 2-cyanomethylsulfinylpyrazine (3a-d).

General Procedure for Preparation of Cinnamonitriles from Benzyl Bromides and 2-Cyanomethylsulfinylpyrazines (3a-d)

A solution of a 2-cyanomethylsulfinylpyrazine (3a-d) (1 mmol), dissolved in DME (10 ml), was added to a DME suspension of sodium hydride (1.2 eq.) (10 ml). After the mixture was stirred for about 10 min, benzyl bromide (1 mmol), following dissolution in DME (10 ml), was added to the mixture dropwise. The solution was refluxed for 15 min and the solvent evaporated off *in vacuo*. The residual solid was extracted with Et_2O. The Et_2O layer was washed with H_2O and dried over Na_2SO_4, followed by evaporation of the solvent. The residue was purified by liquid chromatography, using Kieselgel 60 (230-400 mesh, Merck) as the packing material and a mixture of hexane-Et_2O (30:1) as the developing solvent, under a pressure of 2.0 kg/cm^2 to give a cinnamonitrile.

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