Reaction of 5-(3,4-Dimethoxyphenyl)pyrazine-2,3-dicarbonitrile with Alcohol in the Presence of Base

Koichi Tsuzuki and Masaru Tada*

Department of Chemistry, School of Science and Engineering,
Waseda University, Shinjuku, Tokyo 160, Japan

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5-(3,4-Dimethoxyphenyl)pyrazine-2,3-dicarbonitrile reacts with methanol to give addition products, 3-methoxyiminopyrazine-2-carbonitrile and 2-methoxyiminopyrazine-3-carbonitrile derivatives, and/or substitution products, 3-methoxypyrazine-2-carbonitrile and 2-methoxypyrazine-3-carbonitrile derivatives. The selectivity between the addition and substitution depends on solvent polarity, base, and reaction time. The experimental results are accounted for by the equilibrium between the starting dinitrile and the addition products, methoxyiminopyrazine.

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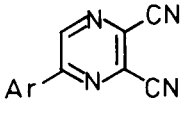
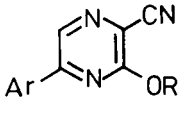
We have studied the thermal [1a-b] and photochemical reactions [2a-c] of 5-((benzo-15-crown-5)-4'-yl)pyrazine-2,3-dicarbonitrile (**1**) and its reference compound, 5-(3,4-dimethoxyphenyl)pyrazine-2,3-dicarbonitrile (**2**). In the course of these studies we have reported the reactions of those pyrazine derivatives with nucleophiles such as water, alcohol, ammonia, and amine to give the substitution products (*e.g.*, **3a** and **4a** from methanol) [1b]. Otsuka *et al.*, have also reported the nucleophilic substitution of symmetrically substituted pyrazine-2,3-dicarbonitriles with alcohol in the presence of amines [3]. They obtained iminoester derivatives **5** in some cases, which is an addition product of methanol to a nitrile.

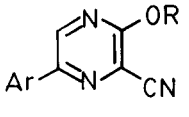
The present study was carried out to clarify these complexities in the reactivity of the pyrazinedicarbonitriles.



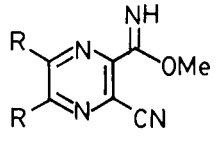
1, Ar:(benzo-15-crown-5)-4'-yl
2, Ar:3,4-dimethoxyphenyl



3a, R:Me
3b, R:Et



4a, R:Me
4b, R:Et



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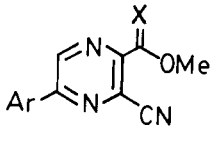
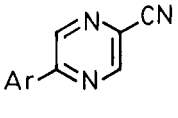
6a, X:NH
6b, X:O



7a, X:NH
7b, X:O



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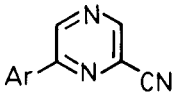

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Treatment of 5-(3,4-dimethoxyphenyl)pyrazine-2,3-dicarbonitrile (**2**) (hereafter Ar denotes 3,4-dimethoxyphenyl in all formulae) in methanol-ethanenitrile (9:1) with triethylamine for 2 hours gave a mixture of two iminoester **6a** and **7a** in nearly quantitative yield. These imino esters are not stable enough for chromatographic separation on silicagel or alumina and the mixture was treated with hydrochloric acid to afford methyl esters **6b** and **7b** (*ca.* 3:1) in 94% yield. Chromatographic separation of the mixture on silicagel gave **6b** and **7b** in the pure state. pyrazinemonocarbonitriles **8** and **9** [2c] were obtained from **6b** and **7b**, respectively, by heating the wet dimethylformamide solution in the presence of lithium iodide [4]. These transformations suggested the structures **6b** and **7b**, and hence those of **6a** and **7a**. Other bases than triethylamine showed the similar catalytic effect and the results are listed in Table 1. Lower yields of **6b** and **7b** by potassium carbonate and potassium *t*-butoxide are compensated by the faster formation of **3a** and **4a** compared to the case of triethylamine catalysis.

Table 1

The Reaction of **2** in Methanol-Ethanenitrile (9:1)

Base	Reaction time (hours)	**6b** and **7b** (Yield %)
K_2CO_3	1.0	57
t-BuOK	1.0	68
DBU	1.0	79
Et_3N	2.0	94

Detailed analyses of those reaction products from **2** and methanol showed the formation of substitution products **3a** and **4a** in minor amounts. Compounds **3a** and **4a** were obtained by the treatment of **2** in methanol-ethanenitrile (1:9) containing potassium carbonate, potassium *t*-butoxide, or DBU (Table 2). The longer reaction time gave more substitution products **3a** and **4a** with concomitant decrease of **6b** and **7b**.

Table 2

The Reaction of **2** in Methanol-Ethanenitrile (1:9)

Base	Reaction time (hours)	**3a** and **4a** (Yield %)	**3a/4a**	**6b** and **7b** (Yield %)
K_2CO_3	1.0	51	2.1	33
	24	61	2.4	0
t-BuOK	1.0	62	2.4	0
	24	69	3.3	0
DBU	1.0	49	2.1	43
	24	67	2.4	0
Et_3N	24 [a]	18	2.0	11

[a] The starting material **2** was recovered in 45% under these conditions.

Those experimental findings suggest the existence of the fast equilibrium between **2** and iminoesters **6a** and **7a**, as reported for benzocarbonitriles having electron attracting substituents [5] and slow substitution of **2** with methanol as depicted in Scheme I. The mixture of methyl iminoesters **6a** and **7a** were heated for 20 hours in ethanol-ethanenitrile (6:1) in the presence of triethylamine to afford the substitution products **3b** (16%) and **4b** (8%) besides the ethyl iminoesters **10a** and **11a** which were isolated after conversion to ethyl esters **10b** and **11b** by acid treatment. Figure 1 shows the time profile of the disappearance of starting material **2**, the formations of iminoesters **6a** and **7a** and substitution products **3a** and **4a**, obtained by the hplc analysis of the reaction mixture.

The nucleophilic substitution takes place through an addition-elimination mechanism which involves the intermediate having no aromatic character of pyrazine [6]. The addition of methanol to the nitrile group, on the other hand, does not destroy the aromatic system. The activation energy of the substitution must be higher than that of iminoester formation and this difference in the activation energy induces the observed difference in reaction rate.

The substitution reaction has the polar transition state of higher energy and therefore the substitution is expected to be slower in a less polar solvent. Indeed the reaction in methanol suspension in the presence of triethylamine gave only iminoesters **6a** and **7a** even after prolonged reaction time. It is conceivable that the substitution products **3a** and **4a** were formed by the direct displacement of the iminoester group by methoxide. However, the electronegativity of the iminoester group must be smaller than that of ester group which is in turn smaller than nitrile group [7], and it is hardly possible that the methoxide ion attacks the pyrazine carbon bearing the iminoester group. Hard bases such as potassium carbonate and potassium *t*-butoxide cause faster substitution reaction than triethylamine, a soft base (see Table 1). This result can be accounted for by the rapid conversion of iminoesters **6a** and **7a**

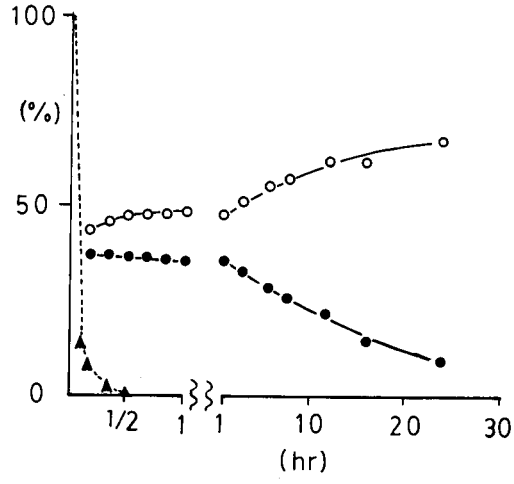
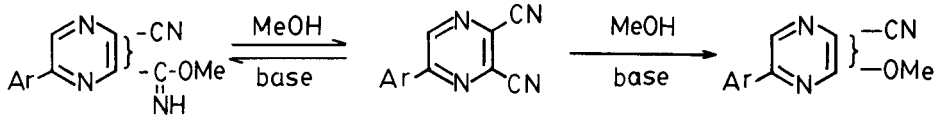
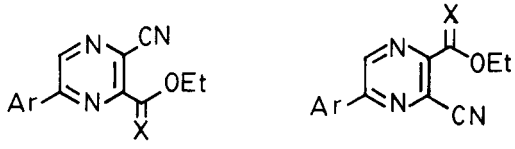


Figure 1. Reaction of **2** with methanol in ethanenitrile-methanol (9:1) in the presence of DBU. O-O: **(3a + 4a)**, ●-●: **(6b + 7b)**, ▲-▲: **2**.



Scheme I



10a, X:NH
10b, X:O

11a, X:NH
11b, X:O

pyrazinedicarbonitrile **2** due to the larger affinity of hard base to the imino-hydrogen and rapid regeneration of the dinitrile. All the experimental findings and discussions support the reaction Scheme I presently proposed.

EXPERIMENTAL

The Reaction of **2** with Methanol under Basic Conditions. a) Reaction in Methanol-Ethanenitrile (9:1).

One of the bases (2.0 mmoles) was added to a solution of **2** (0.5 mmole) in 50 ml of mixed solvent in dry ethanenitrile-freshly distilled methanol (9:1) and the mixture was stirred at room temperature for the period shown in Table 1. The mixture was then treated with 1 ml of 5*N* hydrochloric acid and stirred for 10 minutes. The reaction products were extracted with dichloromethane (10 ml × 4) after condensation of the reaction solution *in vacuo* and dilution with 10 ml of water. Evaporation of the extract after drying over sodium sulfate gave **6b** and **7b** as the main products in the yields listed in Table 1 in addition to trace amount of by-products **3a** and **4a**.

Compounds **6b** and **7b** were separated by preparative tlc on silicagel and eluted by benzene-chloroform-ethyl acetate (1:1:1) and recrystallized from methanol.

Compound **6b**.

This compound had mp 211°; ir (nujol mull): 2240, 1753 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ (J in Hz), 3.98 (s, 3H), 4.01 (s, 3H), 4.11 (s, 3H), 6.97 (d, J = 9, 1H), 7.65-7.90 (m, 2H), 9.16 (s, 1H).

Anal. Calcd. for $C_{15}H_{13}N_3O_4$: C, 60.19; H, 4.38; N, 14.04. Found: C, 59.91; H, 4.44; N, 13.83.

Compound **7b**.

This compound had mp 221°; ir (nujol mull): 2248, 1727 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ (J in Hz), 3.99 (s, 1H), 4.01 (s, 3H), 4.11 (s, 3H), 6.95 (d, J = 9, 1H), 7.75-7.80 (m, 2H), 9.21 (s, 1H).

Anal. Calcd. for $C_{15}H_{13}N_3O_4$: C, 60.19; H, 4.38; N, 14.04. Found: C, 60.36; H, 4.36; N, 14.01.

b) Reaction in Methanol-Ethanenitrile (1:9).

The reaction was carried out in essentially the same manner as in a) of this section except for the solvent system. The main products from these reactions, however, are substitution products **3a** and **4a** instead of **6b** and **7b**. The yields were determined from the relative intensities of the ^{1}H-nmr signals due to the hydrogen on the pyrazine ring using dibromomethane as an internal standard. The yields and reaction conditions are listed in Table 2. Pure **3a** and **4a** were obtained by preparative tlc on alumina (benzene-chloroform, 1:1) and identified by comparison with the authentic samples [2c].

The Preparation of Iminoesters **6a** and **7a** from **2** by the Addition of Methanol.

Triethylamine (15 mmoles) was added to the suspension of **2** (4.6 mmoles) in 100 ml of methanol and the mixture was stirred at room temperature for 6 hours. Analysis (tlc) showed the disappearance of the starting **2** and the generation of **6a** and **7a**. Filtration of the mixture and washing of the precipitate with methanol gave a mixture of **6a** and **7a** in 90% yield. Compounds **6a** and **7a** were decomposed on any chromatographic separation and the product mixture was used for further use without separation into **6a** and **7a**.

Compounds **6a** + **7a**.

This mixture had ir (chloroform): 3300, 2247, 1651 cm^{-1}; ^{1}H-nmr (deuteriochloroform): (J in Hz), 3.97 (s, 3H), 3.99 (s, 3H), 4.13 (s, 3H), 6.96 and 6.98 (d, J = 9, 1H), 7.50-7.80 (m, 2H), 9.02 (diffuse s, 1H), 9.15 and 9.25 (broad s, 1H).

Reaction of Iminoester **6a** and **7a** with Ethanol.

Iminoester **6a** and **7a** (total 0.3 mmole) were dissolved in 35 ml of a mixed solvent composed of dry ethanenitrile-ethanol (1:6) and the mixture was refluxed for 20 hours after the addition of triethylamine (1.5 mmoles). The reaction mixture was treated with 0.5 ml of concentrated hydrochloric acid and stirred for 30 minutes. The condensate of the reaction mixture was passed through a short column of silicagel using chloroform-ethyl acetate (1:1) to remove polar unknown degradation products.

The product mixture thus obtained was subjected to preparative tlc separation on silicagel (chloroform) to give **3b** (16%), **4b** (8%), and the mixture of ethyl esters **10b** and **11b**. Compounds **10b** and **11b** were separated by preparative tlc on silicagel eluted with benzene-chloroform-ethyl acetate (1:1:1).

Compound **3b**.

This compound had mp 190°; ir (chloroform): 2238 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ (J in Hz), 1.49 (t, J = 7, 3H), 3.95 (s, 6H), 4.62 (q, J = 7, 2H), 6.95 (d, J = 9, 1H), 7.54-7.73 (m, 2H), 8.61 (s, 1H).

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.08; H, 5.30; N, 14.51.

Compound **4b**.

This compound had mp 173°; ir (chloroform): 2247 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ (J in Hz), 1.48 (t, J = 7, 3H), 3.92 (s, 3H), 3.96 (s, 3H), 4.56 (q, J = 7, 2H), 6.92 (d, J = 9, 1H), 7.33-7.48 (m, 2H), 8.65 (s, 1H).

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.11; H, 5.36; N, 14.74.

Compound **10b**.

This compound had mp 154°; ir (nujol mull): 2240, 1729 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ (J in Hz), 1.53 (t, J = 7.5, 3H), 3.97 (s, 3H), 4.00 (s, 3H), 4.60 (q, J = 7.5, 2H), 7.02 (d, J = 9, 1H), 7.65-7.90 (m, 2H), 9.18 (s, 1H).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.38; H, 4.96; N, 13.79.

Compound **11b**.

This compound had mp 180°; ir (nujol mull): 2247, 1724 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ (J in Hz), 1.50 (t, J = 7.5, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 4.57 (q, J = 7.5, 2H), 7.00 (d, J = 9, 1H), 7.60-7.85 (m, 2H), 9.21 (s, 1H); ms: Calcd. for $C_{16}H_{15}N_3O_4$: M^+/z = 313.1062. Found: M^+/z = 313.1051.

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.75; H, 5.01; N, 13.07.

Time Profile of the Reaction of **2** with Methanol.

A mixture of **2** (15 mmoles) and DBU (75 mmoles) in 300 ml of mixed solvent of ethanenitrile-methanol (9:1) was stirred at room temperature, and the aliquotes (5 ml) were taken after the intervals. Each aliquot was treated with 0.5 ml fo 5*N* hydrochloric acid and allowed to stand for 10 minutes. After condensation 10 ml of water was added to the residue and extracted twice with dichloromethane (20 ml, 10 ml). Evaporation of the extract after drying over sodium sulfate gave a mixture of substitution products, **3a** and **4a**, and addition products, **6b** and **7b**. The yields of these products were determined by hplc analysis (DuPont Zorbax ODS, 4.6 (φ) × 150 mm, ethanenitrile-water, (2:3) using methyl cinnamate as an internal standard and the results are shown in Figure 1.

Demethoxycarbonylation of Methyl Esters **6b** and **7b**.

Small amount of water (200 μl) was added to the mixture of **6b** (0.3 mmole) and lithium iodide trihydrate (1.7 mmoles) in 8 ml of DMF and the mixture was heated to reflux under Argon for 3 hours. After cooling the mixture was diluted with 100 ml of water and extracted with dichloromethane (50 ml × 3). The extract was condensed under reduced pressure after drying over sodium sulfate and the residual DMF was removed by vacuum distillation. The residue thus obtained was subjected to preparative tlc on silicagel (benzene-chloroform-ethyl acetate, 1:1:1) to afford pyrazinemonocarbonitrile derivative **8** in 44% yield.

Compound **8**.

This compound had mp 141-143°; ir (chloroform): 2245 cm^{-1}; ^1H-nmr (deuteriochloroform): δ (J in Hz), 3.96 (s, 3H), 3.98 (s, 3H), 7.01 (d, J = 9, 1H), 7.59-7.75 (m, 2H), 8.87 (d, J = 2, 1H), 9.09 (d, J = 2, 1H).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 65.05; H, 4.64; N, 17.16.

The same treatment of **7b** gave pyrazinecarbonitrile derivative **9** in 38% yield.

Compound **9**.

This compound had mp 179-180°; ir (chloroform): 2250 cm^{-1}; ^1H-nmr (deuteriochloroform): δ (J in Hz), 3.96 (s, 3H), 4.01 (s, 1H), 7.04 (d, J = 9, 1H), 7.56-7.70 (m, 2H), 8.75 (s, 1H).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.91; H, 4.67; N, 17.19.

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