# One-step Preparation of 3-Alkoxypyrazine-2-carbonitriles from Pyrazine-2,3-dicarbonitriles and Related Reactions



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A series of 5,6-disubstituted 3-alkoxypyrazine-2-carbonitriles (**2a-i**) were prepared from 5,6-disubstituted pyrazine-2,3-dicarbonitriles (**1a-d**) by direct substitution with alcohols. Treatment of **1** with amines gave either pyrrolopyrazines (**3a,b**) or substitution products (**4,5**). In a low temperature range, **1** afforded imidates and related compounds (**6-11**). The preference among these reactions depended on the 5,6-substituents and on the reaction conditions.

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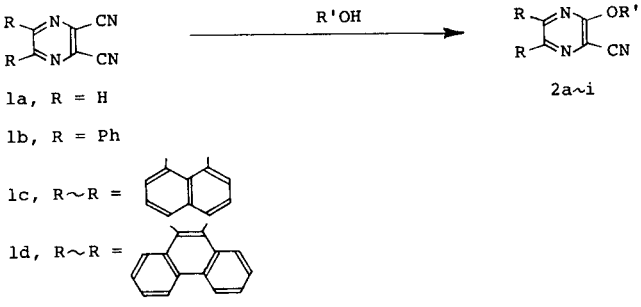
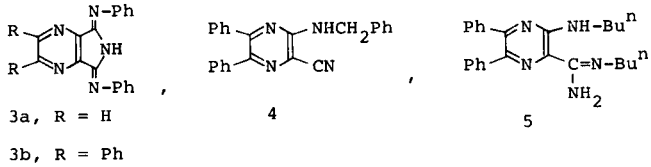
Derivatives of 3-methoxypyrazine-2-carboxylic acid are known to possess powerful antimicrobial activity (1). During the course of our study on heterocyclic synthesis starting from diaminomaleonitrile (DAMN) (2), we found a new substitution reaction of pyrazine-2,3-dicarbonitriles (**1**) to give 3-alkoxypyrazine-2-carbonitriles (**2**), the precursors to potentially bioactive 3-alkoxypyrazine-2-carboxylic acid derivatives (1,3). Pyrazine-2,3-dicarbonitrile and its 5,6-disubstituted compounds can be prepared from DAMN and α-diketones (5a,6).




The substitution reaction was accomplished by heating **1a-d** with an excess amount of alcohols in polar aprotic media (Table I). The effect of catalysts on the reaction varied depending on the reactants used. The survey with the reaction of **1a** and ethanol in *N,N*-dimethylformamide (DMF) showed the apparent catalytic effect of several bases (Table II). On the other hand, addition of a base in the reactions of **1b-d** generally induced side-reactions to decrease the yields and purity of the products. The effect of calcium chloride was also dependent on the reaction in question. The reaction of **1a** and 1-butanol was found to be promoted by the catalyst, when it was compared between the formation of a 16% yield of **2c** after heating with calcium chloride in DMF for 2 hours and the complete recovery of **1a** by the control reaction in the absence of the catalyst. Excellent yields of **2d** and **2g** were obtained by smooth reactions of **1b** without any catalyst. In other reactions of **1b-d**, the addition of calcium chloride gave slightly improved results. As shown in Table I, most reactions required a polar aprotic solvent (DMF or dimethylsulfoxide). When the reaction was carried out in the absence of these solvents the starting materials were recovered unchanged.

There are two other reactions of **1** with nucleophilic reagents which occur under related reaction conditions with the above substitutions. When a mixture of **1a**, aniline, calcium chloride (7) and DMF was heated under reflux, pyrrolopyrazine **3a** was obtained in a 85% yield. The reaction of **1b** with aniline proceeded more sluggishly to give a 10% yield of **3b** along with the unchanged starting pyrazine (a 12% recovery). Similar treatment of **1c** and **1d** with aniline, calcium chloride and 1-butanol gave the substitution products, **2h** and **2i**, respectively (Table I). Benzylamino compound **4** was obtained from benzylamine and **1b** in a 17% yield. 1-Butylamine underwent further reaction with **1b** to give butylaminoamidine **5** in a 71% yield.

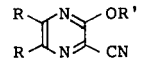


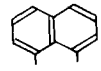
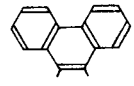

In the low temperature range, pyrazine-2,3-dicarbonitriles react with alcohols in the presence of bases to give imidates. Reaction of **1a**, methanol and a catalytic amount of sodium methoxide at room temperature gave diimidate **6** in a 64% yield. The corresponding monoimidate was not detected when the reaction was carried out at lower temperature and in shorter reaction time. Treatment of **6** with hydrogen chloride gave a mixture of diamide **7** (a 16% yield) and carbamoylester **8** (a 15% yield).

*0022-152X/80/030455-05$02.25*

Table I

3-Alkoxypyrazine-2-carbonitriles



| Compound | R | R' | Catalyst | Solvent (a) | Reaction time hours (b) | % Yield |
|---|---|---|---|---|---|---|
| **2a** | H | Me | $Et_3N$ | DMF | 16 | 30 |
| **2b** | H | Et | $Et_3N$ | DMSO | 9 | 51 |
| **2c** | H | *n*-Bu | $Et_3N$ | DMF | 2.5 | 53 |
| **2d** | Ph | Me | none | DMF | 26 | 85 |
| **2e** | Ph | Et | NaOEt | EtOH | 3 (30-40°) | 53 |
| **2f** | Ph | *n*-Bu | $CaCl_2$ | DMF | 24 | 74 |
| **2g** | Ph | $CH_2CH_2OH$ | none | DMF | 11 (150°) | 89 |
| **2h** |  | *n*-Bu | $CaCl_2$ | DMF | 24 | 40 |
| **2i** |  | *n*-Bu | $CaCl_2$ | DMF | 48 | 90 |

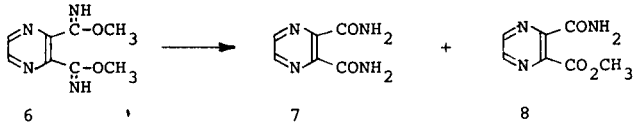
(a) DMF, *N,N*-dimethylformamide; DMSO, dimethylsulfoxide. (b) The reaction was carried out at the boiling temperature of the alcohol unless specially cited.

Table II

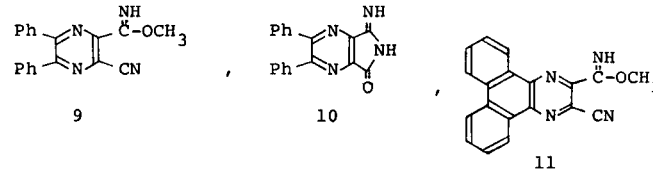
A Survey of Catalyst for the Reaction of Pyrazine-2,3-dicarbonitrile (**1a**) and Ethanol (a)

| Catalyst | Reaction time, hours | Substitution product, % | Recovery of pyrazine **1a**, % |
|---|---|---|---|
| sodium 2,6-di-*t*-butylphenoxide | 4 | 57 | 21 |
| triethylamine | 14 | 50 | 0 |
| sodium cyanide | 0.8 | 51 | 0 |
| morpholine | 14 | 44 | 10 |
| triethylenediamine | 14 | 37 | 45 |
| pyridine | 14 | 7 | 65 |
| curpic chloride | 12 | 0 | 12 |

(a) The mixture (**1a**, 0.4 g., ethanol, 15 ml., DMF, 5 ml., catalyst, 0.1-0.07 g.) was heated under ethanol reflux.



6 7 8



9 10 11

The reaction of **1b** (R = Ph) and methanol with aqueous sodium hydroxide at 0-5° gave a 75% yield of monoimidate **9**. When the reaction was carried out at room temperature, a cyclized product **10** was obtained in 16% yield. The same compound **10** was also obtained in almost quantitative yield from 3-cyano-5,6-diphenylpyrazine-2-carboxamide (2) and methanol in the presence of sodium methoxide. The reaction of **1d** and methanol with sodium methoxide afforded the monoimidate **11**. No diimidate was detected by treatment of **1b** and **1d** under various reaction conditions. 5,6-Dimethylpyrazine-2,3-dicarbonitrile has been known to afford the monoimidate by the reaction with ethanol in the presence of hydrogen chloride catalyst. (8).

To obtain some mechanistic outlook on the formation of **2** from **1**, imidate **9** was treated under similar conditions to those for the preparation of **2f** from **1b**. Thus, a mixture of a 5.6% yield of **2d** and a 6.1% yield of **2f** was obtained from **9** and 1-butanol in DMF by heating under reflux for 26 hours. A similar treatment of **9** with methanol gave **2d** in a 3.8% yield. The small yields relative to those of the direct conversion of **1b** into **2d** and **2f** (23% and 74% yield, respectively) indicate that the monoimidate **9** is not the possible intermediate for the main path of the substitution reaction. As shown above, the addition reaction of methanol to **1** affords either mono- or diimidates. In con-

trast, only one nitrile group is replaced by the substitution reaction of **1**. The reaction feature of the latter reaction suggests the mechanism by direcct replacement of a nitrile group in **1** with an alkoxide anion. However, the path through an imidate intermediate could not be excluded, since the above experiments showed the formation of almost equal amounts of **2d** and **2f** by the reaction of **9** with a large excess of 1-butanol.

Although there are some limitations depending on the substituents R and on the reaction conditions, the present synthesis of 3-alkoxypyrazine-2-carbonitriles will be useful for the preparations of pyrazine and pteridine derivatives.

## EXPERIMENTAL (9)

Materials.

Pyrazine-2,3-dicarbonitrile (**1a**) and its 5,6-disubstituted derivatives (**1b-d**) were prepared from diaminomaleonitrile (DAMN) and α-diketones (5a,6) and were confirmed by analytical and spectral data.

3-Methoxypyrazine-2-carbonitrile (**2a**).

A mixture of 0.30 g. of **1a**, 0.1 ml. of triethylamine, 15 ml. of methanol and 5 ml. of *N,N*-dimethylformamide (DMF) was heated under reflux for 16 hours. After concentration under reduced pressure, the residue was dissolved in water and the solution was extracted with ethyl acetate. Concentration of the extract gave 0.32 g. of red-brown oil, which was subjected to column chromatographic purifications (silica gel/ethyl acetate-chloroform) to give 0.12 g. (a 30% yield) of **2a**, as colorless needles, m.p. 54-55° (reference 1a, m.p. 56°); ir (potassium bromide): 2235, 1532, 1490, 1395, 1318, 1191, 1172, 1143, 998, 864 $cm^{-1}$; MS (m/e) 135 (100%, $M^+$); nmr (deuteriochloroform): δ 4.10 (s, 3H, $OCH_3$), 8.25 (d, J = 2 Hz, 1H, ring H), 8.33 (d, J = 2 Hz, 1H, ring H).

3-Ethoxypyrazine-2-carbonitrile (**2b**).

A mixture of 0.39 g. of **1a**, 0.10 g. of sodium 2,6-di-*t*-butylphenoxide, 15 ml. of ethanol and 5 ml. of DMF was heated under reflux for 2 hours. Then the base catalyst was quenched by the addition of 0.057 g. of pyridine hydrochloride and the solution was concentrated under reduced pressure. The residue was treated by the procedure described above to give 0.26 g. of **2b**, m.p. 43-44° (from aqueous ethanol) as colorless crystals; ir (potassium bromide): 2230, 1528, 1411, 1381, 1341, 1312, 1177, 1140, 1019, 865 $cm^{-1}$; ms: (m/e) 149 (29%, $M^+$), 93 (100%).

*Anal.* Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.17. Found: C, 56.32; H, 4.68; N, 28.16.

3-*n*-Butoxypyrazine-2-carbonitrile (**2c**).

This compound was prepared by the above procedure from **1a** (0.39 g.), triethylamine (0.15 ml.), 1-butanol (10 ml.) and DMF (5 ml.), colorless oil; ir (neat): 2045, 1532, 1425, 1319, 1180, 1142 $cm^{-1}$; nmr (deuteriochloroform): δ 0.97 (t, J = 6 Hz, 3H, $CH_3$), 1.7 (m, 4H, $CH_2$), 4.45 (t, J = 6 Hz, 2H, $OCH_2$), 8.20 (d, J = 2 Hz, 1H, ring H), 8.29 (d, J = 2 Hz, 1H, ring H); ms: (m/e) 177 (10%, $M^+$), 56 (100%).

3-Methoxy-5,6-diphenylpyrazine-2-carbonitrile (**2d**).

A mixture of 0.564 g. of **1b**, 5 ml. of methanol and 5 ml. of DMF was refluxed for 26 hours and was concentrated under reduced pressure to give about 1 ml. of tan oil. The crude product **2d** was precipitated by addition of 10 ml. of water to the residue. The column chromatographic purification (silica gel/ethyl acetate-*n*-hexane) gave 0.499 g. of **2d**, m.p. 165-167°; ir (potassium bromide): 2240, 1538, 1460, 1385, 1335, 1197, 1178, 1015, 940.

*Anal.* Calcd. for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.63. Found: C, 75.00; H, 4.48; N, 14.25.

3-Ethoxy-5,6-diphenylpyrazine-2-carbonitrile (**2e**).

A mixture of 5.0 g. of **1b** and 1.63 g. of sodium ethoxide in 50 ml. of ethanol was stirred at 30-40° for 3 hours. The insoluble material was separated by filtration and the filtrate was concentrated under reduced pressure to a 1/5 volume. The viscous solution was kept for 4 days to give 2.80 g. of the product **2e** as pale-green crystals, m.p. 148-150°; ir (potassium bromide): 3040, 2975, 2220, 1530, 1417, 1375, 1345, 1318, 1170, 1015, 690 $cm^{-1}$.

*Anal.* Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.29; H, 4.97; N, 13.77.

3-*n*-Butoxy-5,6-diphenylpyrazine-2-carbonitrile (**2f**).

This compound was prepared after the procedure described above for the preparation of **2d**, m.p. 134-136°; ir (potassium bromide): 3060, 2960, 2930, 2875, 2235, 1535, 1425 $cm^{-1}$.

*Anal.* Calcd. for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.11; H, 5.75; N, 12.65.

3-β-Hydroxyethoxy-5,6-diphenylpyrazine-2-carbonitrile (**2g**).

This compound was prepared by the procedure described above for the preparation of **2d**, m.p. 140-141°; ir (potassium bromide): 3070, 3020, 2950, 2230, 1535, 1375, 1395, 1355, 1325, 760, 700 $cm^{-1}$; ms: (m/e) 317 ($M^+$).

*Anal.* Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.76; H, 4.79; N, 13.05.

9-*n*-Butoxyacenaphtho[1,2-*b*]pyrazine-8-carbonitrile (**2h**).

A mixture of 0.51 g. of **1c**, 0.41 g. of aniline, 0.02 g. of calcium chloride, 20 ml. of 1-butanol and 20 ml. of DMF was heated at 150° for 24 hours. After filtration of the resulting solid (**2h**), the filtrate was concentrated under reduced pressure and the residue was poured into 100 ml. of water to give an additional crop (total 40% yield), 193-194° (from acetone); ir (potassium bromide): 2960, 2925, 2870, 2230, 1615, 1550, 1325 $cm^{-1}$; ms: (m/e) 301 ($M^+$).

*Anal.* Calcd. for $C_{19}H_{15}N_3O$: C, 75.73; H, 5.02; N, 13.94. Found: C, 75.96; H, 5.01; N, 13.81.

3-*n*-Butoxydibenzo[*f,h*]quinoxaline-2-carbonitrile (**2i**).

This compound was prepared by the procedure described above, m.p. 181-183° (from acetone); ir (potassium bromide): 2960, 2870, 2230, 1610, 1540 $cm^{-1}$; ms: (m/e) 327 ($M^+$).

*Anal.* Calcd. for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 76.76; H, 5.17; N, 12.65.

5,7-Bis(phenylamino)-5*H*-6,7-dihydropyrrolo[3,4-*b*]pyrazine (**3a**).

A mixture of 0.65 g. of **1a**, 0.98 g. of aniline, 0.06 g. of anhydrous calcium chloride and 25 ml. of 1-butanol was heated under reflux for 48 hours. The mixture was concentrated under reduced pressure and the residue was dissolved in 30 ml. of water. Extraction with chloroform (80 ml.) and evaporation of the chloroform extracts, after washing with water and drying, gave 1.27 g. (a 85% yield) of red-brown crystals. The analytical sample was prepared by recrystallization from aqueous ethanol: orange crystal, m.p. 209-210°; ir (potassium bromide): 1610, 1557, 1503, 1135, 755, 742 $cm^{-1}$; nmr (deuteriochloroform + DMSO-$d_6$): δ 7.5 (m, 10H, phenyl H), 8.7 (broad s, 2H, pyrazine-H), 10.7 (broad s, 1H, N*H*).

*Anal.* Calcd. for $C_{18}H_{13}N_5$: C, 72.22; H, 4.38; N, 23.40. Found: C, 72.01; H, 4.20; N, 23.44.

2,3-Diphenyl-5,7-bis(phenylimino)-5*H*-6,7-dihydropyrrolo[3,4-*b*]pyrazine (**3b**).

A mixture of 0.56 g. of **1b**, 0.42 g. of aniline, and 0.02 g. of calcium chloride in 17 ml. of DMF was heated at 150° for 24 hours, and concentrated under reduced pressure. The residue was washed with water (50 ml.) and the organic layer (viscus oil) was crystallized from ethanol. The solid was dissolved in chloroform and was applied to column chromatography (silica gel/chloroform) to give 0.066 g. (11.7% recovery) of unreacted **1b** and 0.091 g. (10.1% yield) of **3b** as yellow crystals. The analytical sample, m.p. 275-276° dec. (from benzene); ir (potassium

bromide): 3060, 1603, 1560, 1510, 1355, 690 $cm^{-1}$.

*Anal.* Calcd. for $C_{30}H_{21}N_5$: C, 79.80; H, 4.69; N, 15.51. Found: C, 79.58; H, 4.62; N, 15.21.

3-Benzylamino-5,6-diphenylpyrazine-2-carbonitrile (**4**).

A mixture of 0.35 g. of **1b**, 0.27 g. of benzylamine and 10 ml. of DMF was heated at 150° for 14 hours and concentrated under reduced pressure. The residue was passed through a column (silica gel/*n*-hexane:ethyl acetate = 5:1) to give **4** as colorless crystals, m.p. 160-161°; ir (potassium bromide): 3375, 3060, 3030, 2930, 2220, 1580, 1570, 1535, 1375, 1195, 700 $cm^{-1}$; ms: (m/e) 362 ($M^+$).

*Anal.* Calcd. for $C_{24}H_{18}N_4$: C, 79.54; H, 5.01; N, 15.46. Found: C, 79.39; H, 4.98; N, 15.16.

2-*n*-Butylamino-5,6-diphenylpyrazine-3-*N*-*n*-butylamidine (**5**).

A mixture of 0.564 g. of **1b**, 5 ml. of *n*-butylamine and 5 ml. of DMF was refluxed for 23 hours. After concentration under reduced pressure, the residue was treated with diethyl ether. The ether solution was washed with water for several times and dried with magnesium sulfate. The evaporated residue (dark red oil) was purified by column chromatography (silica gel/*n*-hexane:ethyl acetate = 15:1-9:1) to give 0.567 g. (a 70.7% yield) of yellow needles. Recrystallization from petroleum ether gave the analytical sample, m.p. 76-77°; ir (potassium bromide): 3475, 3370, 3060, 2950, 2925, 2870, 1645, 1585, 1570, 1480, 1180, 775, 700 $cm^{-1}$; nmr (deuteriochloroform): $\delta$ 7.6-7.1 (m, 10H, phenyl-H), 6.8-5.4 (broad peaks, 2H, N*H*), 3.75-3.35 (m, 2H, N-C$H_2$), 3.35-3.00 (m, 2H, =N-C$H_2$), 2.00-0.75 (m, 15H, alkyl-H plus N*H*); ms: (m/e) 401 ($M^+$).

*Anal.* Calcd. for $C_{25}H_{31}N_5$: C, 74.78; H, 7.78; H, 17.44. Found: C, 74.82; H, 7.69; N, 17.25.

Dimethyl Pyrazine-2,3-dicarboimidate (**6**).

A solution of 0.65 g. of **1a**, 0.014 g. of sodium methoxide in 80 ml. of methanol was stirred at room temperature for 18 hours, and concentrated. The residue was crystallized from ether and *n*-hexane to give a tan solid. The crude product was dissolved in 80 ml. of ethyl acetate, and treated with charcoal. Filtration and addition of *n*-hexane to the filtrate gave 0.68 g. (a 64% yield) of **6**. Recrystallization from chloroform and *n*-hexane gave colorless needles, m.p. 138-140° dec; ir (potassium bromide): 3355, 1681, 1588, 1373, 1182, 1080, 860 $cm^{-1}$; nmr (DMSO-$d_6$): $\delta$ 2.40 (s, 6H, C$H_3$), 6.40 (s, 2H, N*H*), 7.60 (s, 2H, ring H).

*Anal.* Calcd. for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.62; H, 5.12; N, 28.75.

A mixture of 1.94 g. of diimidate **6** and 50 ml. of concentrated hydrochloric acid was stirred at room temperature for 8 hours. The resulting precipitate was collected by filtration and washed with methanol. The methanol insoluble solid was identified (by ir) as pyrazine-2,3-dicarbonitrile (**7**, m.p. ~235° dec.) with a 16% yield (10), and the methanol soluble solid (a 15% yield after concentration of the filtrate) was identified as:

Methyl 3-Carbamoylpyrazine-2-carboxylate (**8**).

This compound was obtained as colorless crystal, m.p. 166-169° (from methanol); ir (potassium bromide): 3400, 1745, 1670, 1310, 1100 $cm^{-1}$; nmr (DMSO-$d_6$): $\delta$ 3.85 (s, 3H, C$H_3$), 7.91 and 8.30 (broad peaks, total 2H, N*H*), 8.85 (s, 2H, ring H).

*Anal.* Calcd. for $C_7H_7N_3O_3$: C, 46.41; H, 3.90; N, 23.20. Found: C, 46.33; H, 3.86; N, 23.42.

Methyl 3-Cyano-5,6-diphenylpyrazine-2-carboimidate (**9**).

To an ice-cooled mixture of 1.13 g. of **1b** and 250 ml. of methanol was added 0.22 g. of sodium methoxide. After stirring at 0-5° for 4 hours, the reaction mixture was poured into 1 l. of water to give 0.94 g. (a 75% yield) of **9**. Recrystallization from methanol gave colorless crystals, m.p. 158-160° dec.; ir (potassium bromide): 3380, 3060, 3025, 2940, 2230, 1660, 1525, 1380, 1340, 1130, 1086 $cm^{-1}$; nmr (deuteriochloroform): $\delta$ 4.16 (s, 3H, OC$H_3$), 7.4 (m, 10H, phenyl-H), 9.3 (broad peak, 1H, N*H*).

*Anal.* Calcd. for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.82. Found: C, 72.52; H, 4.42; N, 17.56.

5-Imino-7-oxo-2,3-diphenyl-5*H*-6,7-dihydropyrrolo[3,4-*b*]pyrazine (**10**).

The above reaction was carried out at room temperature. The mixture was concentrated to nearly dryness under reduced pressure. The residue was neutralized with 0.5 *N* aqueous hydrogen chloride (4 ml.). To the resulting solution was added 40 ml. of acetone and the insoluble solid was separated. The filtrate was concentrated to a volume of 20 ml. and cooled to give 0.94 g. (a 16% yield) of white crystals. Recrystallization from ethanol gave colorless crystals, m.p. 260-261°; ir (potassium bromide): 3300, 3150, 3020, 1765, 1675, 1550, 1355, 1170, 1110, 1060, 920, 860, 790, 770, 720, 695; ms: (m/e) 300 ($M^+$).

*Anal.* Calcd. for $C_{18}H_{12}N_4O$: C, 71.99; H, 4.03; N, 18.66. Found: C, 71.85; H, 3.85; N, 18.70.

The same compound **10** was obtained also by the following procedure: A mixture of 30 g. of 3-cyano-5,6-diphenylpyrazine-2-carboxamide (2), 3.0 g. of sodium and 250 ml. of methanol was stirred to complete dissolution. The solution was treated with 0.5 g. of active carbon and neutralized with about 10 ml. of acetic acid to give 29.3 g. of white flakes.

Methyl 3-Cyanodibenzo[*f*,*h*]quinoxaline-2-carboimidate (**11**).

This compound was prepared from 0.50 g. of **1d** and 0.02 g. of sodium methoxide in 50 ml. of methanol by stirring at room temperature for 17 hours. The resulting precipitate was purified by reprecipitation from chloroform and diethyl ether to give pale yellow crystals having no definite m.p. (decomposed over 190°); ir (potassium bromide): 3300, 2945, 2230, 1650, 1603 $cm^{-1}$; nmr (deuteriochloroform): $\delta$ 4.19 (s, 3H, OC$H_3$), 7.77, 8.48 and 9.00 (m, total 8H, aromatic H) 9.37 (broad, 1H, N*H*).

*Anal.* Calcd. for $C_{19}H_{12}N_4O$: C, 73.07; H, 3.87; N, 17.94. Found: C, 73.26; H, 3.87; N, 18.07.

Reactions of Imidate **9** with Alcohols.

a) A mixture of 0.63 g. of **9**, 5 ml. of 1-butanol and 5 ml. of DMF was refluxed for 26 hours. After concentration of the mixture under reduced pressure, the residue was column chromatographed to give a 5.6% yield of **2d** and a 6.1% yield of **2f**.

b) A 3.8% yield of **2d** was obtained from 0.63 g. of **9**, 5 ml. of methanol and 5 ml. of DMF by the treatment described above.

## REFERENCES AND NOTES

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