Hiroshi Maruoka, Fumi Okabe and Kenji Yamagata*

Faculty of Pharmaceutical Sciences, Fukuoka University,
8-19-1 Nanakuma, Jounan-ku, Fukuoka 814-0180, Japan
e-mail: yamagata@fukuoka-u.ac.jp
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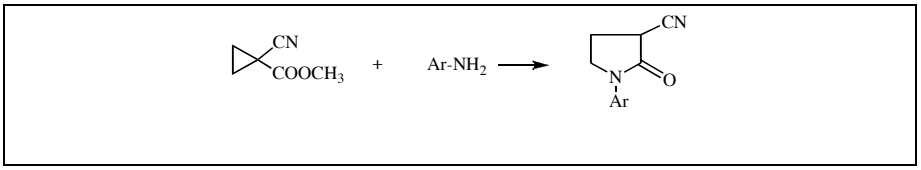

Cyclopropanes substituted at the same ring carbon by two electron-withdrawing groups such as alkoxycarbonyl or cyano group react with the primary arylamines *via* a ring-opening reaction and ensuing intramolecular cyclization to form substituted pyrrolidines.

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INTRODUCTION

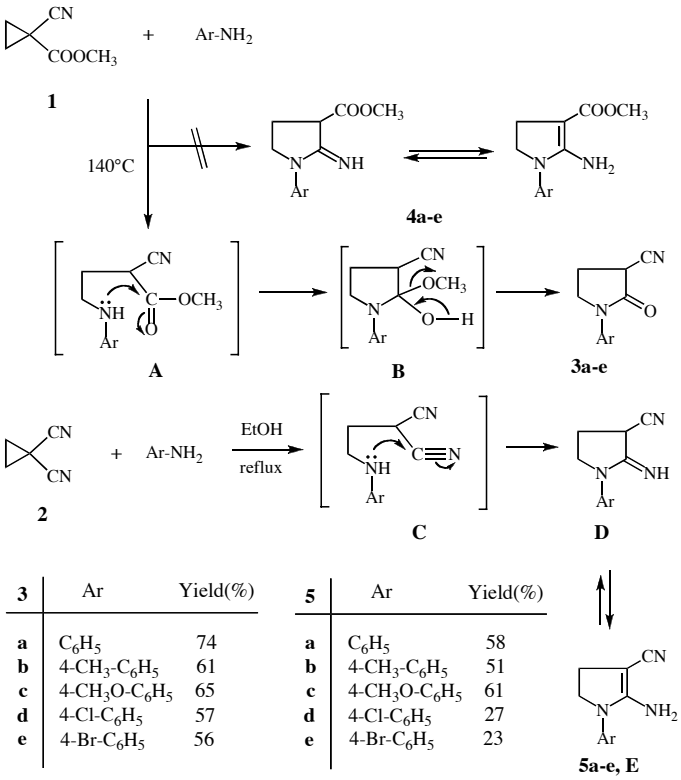
In view of the synthesis of useful five-membered-ring heterocycles, cyclopropanes having at the same ring carbon by two electron-withdrawing groups are potential intermediates [1-8]. In previous papers we described a method leading to excellent yields of 1-acyl-2-oxo-3-pyrrolidinecarbonitriles starting from *N*-acyl-1-cyanocyclopropanecarboxamides [9]. However, under the same conditions, in the case of *N*-aryl (and *N*-alkyl)-1-cyanocyclopropanecarboxamides, a similar ring expansion reaction did not take place. We now describe a simple method for the synthesis of 1-aryl-2-oxo-3-pyrrolidinecarbonitriles (**3a**-**e**) and 1-aryl-2-imino-3-pyrrolidinecarbonitriles (**5a**-**e**) through a reaction of methyl 1-cyanocyclopropanecarboxylate (**1**) [10] and cyclopropane-1,1-dicarbonitrile (**2**) [11] with primary arylamines.

RESULTS AND DISCUSSION

When a mixture of **1** and aniline was directly heated at 140° without solvent, the ring-opening/recyclization product, 2-oxo-1-phenylpyrrolidinecarbonitrile (**3a**) was obtained in 74% yield, and no formation of methyl 2-imino-1-phenylpyrrolidinecarboxylate (**4a**) was observed. Elemental analysis and spectral data of **3a** are consistent with the assigned structure. Compound **1** reacted with 4-substituted anilines (4-methylaniline, 4-methoxyaniline, 4-chloroaniline and 4-bromoaniline) under the same conditions to give the corresponding 1-aryl-2-oxo-3-pyrrolidinecarbonitriles **3b**-**e** in good yields.

The formation of **3** can be explained by the mechanism shown in Scheme. Primary arylamines attack at the 2-position of **1** to form the intermediate secondary arylamines **A**, which then undergo intramolecular cyclization to give **B**. The intermediate **B** is transformed into **3** by elimination of methanol. A similar transformation of cyclopropane

Scheme



3	Ar	Yield(%)
a	C_6H_5	74
b	4-CH_3-C_6H_5	61
c	4-CH_3O-C_6H_5	65
d	4-Cl-C_6H_5	57
e	4-Br-C_6H_5	56

5	Ar	Yield(%)
a	C_6H_5	58
b	4-CH_3-C_6H_5	51
c	4-CH_3O-C_6H_5	61
d	4-Cl-C_6H_5	27
e	4-Br-C_6H_5	23

derivatives has previously been described [6,7]. The weak nucleophilic primary arylamine such as 2-nitroaniline, 3-nitroaniline and 4-nitroaniline did not react with **1** under the same conditions, and **1** was recovered unchanged. On the other hand, the reaction of **1** with a primary aliphatic amine such as benzylamine or cyclohexylamine afforded an inseparable mixture showing many spots on thin-layer chromatography.

Subsequently, we examined the reaction of cyclopropane-1,1-dicarbonitrile **2** with primary arylamines. Treatment of **2**

with primary arylamines (aniline, 4-methylaniline, 4-methoxyaniline, 4-chloroaniline and 4-bromoaniline) in refluxing ethanol gave the corresponding 1-aryl-2-imino-3-pyrrolidinecarbonitriles **5a-e** in fair to good yields. Probably, these reaction take place through the malononitrile derivatives **C**. The ^{1}H nmr spectra of **5a-e** in deuteriochloroform indicate that **5a-e** consist of a tautomeric mixture of the imine **D** and the enamine **E** forms.

However, the reaction of **2** with 2-nitroaniline, 3-nitroaniline or 4-nitroaniline failed, and **2** was recovered unchanged.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on a JASCO FT/IR-230 spectrometer. The ^{1}H nmr and ^{13}C nmr spectra were measured with a JEOL JNM-A500 instrument (500.00 MHz for ^{1}H, 125.65 MHz for ^{13}C) with TMS as internal standard. ^{13}C signal assignments were confirmed by the DEPT techniques. FAB mass spectra were taken with a JEOL JMS-HX100 instrument at 70 eV. Elemental analyses were performed using a YANACO MT-6 elemental analyzer.

General Procedure for the Preparation of 3. A mixture of methyl 1-cyanocyclopropanecarboxylate (2.50 g 20 mmoles) and the arylamine (20 mmoles) was heated at 140° for 4 hours (in the case of aniline, 4-methylaniline and 4-methoxyaniline) or 8 hours (4-chloroaniline and 4-bromoaniline). After cooling, the reaction mixture was purified by column chromatography on silica gel with dichloromethane as the eluent to give **3**.

2-Oxo-1-phenyl-3-pyrrolidinecarbonitrile (**3a**). This compound was obtained as colorless columns (2.76 g, 74%), mp 121-122° (acetone-petroleum ether); ir (potassium bromide): ν 2250 (CN), 1695 cm^{-1}(C=O); ^{1}H nmr (deuteriochloroform): δ, ppm 2.45-2.52 (m, 1H, 4-H), 2.58-2.65 (m, 1H, 4-H), 3.72 (t, J = 9.2 Hz, 1H, 3-H), 3.88-3.96 (m, 2H, 5-H), 7.20-7.60 (m, 5H, aryl H); ^{13}C nmr (deuteriochloroform): δ, ppm 23.6 (C-4), 35.1 (C-3), 46.8 (C-5), 116.7 (CN), 120.2, 125.7, 129.1, 138.1 (C aryl), 164.8 (C-2); ms: m/z 187 [M+H]$^+$. *Anal.* Calcd. for $C_{11}H_{10}N_2O$ (MW 186.2): C, 70.95; H, 5.41; N, 15.04. Found: C, 71.07; H, 5.57; N, 14.94.

1-(4-Methylphenyl)-2-oxo-3-pyrrolidinecarbonitrile (**3b**). This compound was obtained as colorless columns (2.45 g, 61%), m.p. 135-136° (acetone-petroleum ether); ir (potassium bromide): ν 2249 (CN), 1700 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ, ppm 2.29 (s, 3H, CH_3), 2.30-2.40 (m, 1H, 4-H), 2.50-2.60 (m, 1H, 4-H), 3.80-3.85 (m, 2H, 5-H), 4.30 (dd, J = 9.2, 10.4 Hz, 1H, 3-H), 7.20-7.22 (m, 2H, aryl H), 7.50-7.52 (m, 2H, aryl H); ^{13}C nmr (DMSO-d_6): δ, ppm 20.3 (CH_3), 22.7 (C-4), 34.6 (C-3), 46.5 (C-5), 118.1 (CN), 120.0, 129.1, 134.1, 136.1 (C aryl), 165.6 (C-2); ms: m/z 201 [M+H]$^+$. *Anal.* Calcd. for $C_{12}H_{12}N_2O$ (MW 200.3): C, 71.98; H, 6.04; N, 13.99. Found: C, 72.00; H, 6.05; N, 14.00.

1-(4-Methoxyphenyl)-2-oxo-3-pyrrolidinecarbonitrile (**3c**). This compound was obtained as colorless columns (2.80 g, 65%), mp 135-136° (acetone-petroleum ether); ir (potassium bromide): ν 2252 (CN), 1686 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ, ppm 2.40-2.50 (m, 1H, 4-H), 2.55-2.65 (m, 1H, 4-H), 3.70 (t, J = 9.2 Hz, 1H, 3-H), 3.80 (s, 3H, OCH_3), 3.83-3.93 (m, 2H, 5-H), 6.88-6.93 (m, 2H, aryl H), 7.43-7.47 (m, 2H, aryl H); ^{13}C nmr (deuteriochloroform): δ, ppm 23.6 (C-4), 34.9 (C-3), 47.2 (C-5), 55.5 (O-CH_3), 114.3 (C aryl), 116.8 (CN), 122.1, 131.2, 157.5 (C aryl), 164.6 (C-2); ms: m/z 217 [M+H]$^+$. *Anal.* Calcd. for $C_{12}H_{12}N_2O_2$ (MW 216.2): C, 66.65; H, 5.59; N, 12.95. Found: C, 66.65; H, 5.59; N, 12.93.

1-(4-Chlorophenyl)-2-oxo-3-pyrrolidinecarbonitrile (**3d**). This compound was obtained as colorless needles (2.51 g, 57%), mp 120-121° (acetone-petroleum ether); ir (potassium bromide): ν 2250, (CN), 1701 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ, ppm 2.45-2.55 (m, 1H, 4-H), 2.60-2.67 (m, 1H, 4-H), 3.74 (t, J = 9.2 Hz, 1H, 3-H), 3.85-3.95 (m, 2H, 5-H), 7.30-7.40 (m, 2H, aryl H), 7.50-7.60 (m, 2H, aryl H); ^{13}C nmr (deuteriochloroform): δ, ppm 23.5 (C-4), 35.1 (C-3), 46.7 (C-5), 116.4 (CN), 121.3, 129.2, 131.1, 136.7 (C aryl), 164.9 (C-2); ms: m/z 221 [M+H]$^+$. *Anal.* Calcd. for $C_{11}H_9ClN_2O$ (MW 220.7): C, 59.88; H, 4.11; N, 12.70. Found: C, 59.96; H, 4.15; N, 12.66.

1-(4-Bromophenyl)-2-oxo-3-pyrrolidinecarbonitrile (**3e**). This compound was obtained as colorless scales (2.99 g, 56%), mp 133-134° (acetone-petroleum ether); ir (potassium bromide): ν 2251 (CN), 1700 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ, ppm 2.45-2.55 (m, 1H, 4-H), 2.60-2.67 (m, 1H, 4-H), 3.73 (t, J = 9.2 Hz, 1H, 3-H), 3.85-3.95 (m, 2H, 5-H), 7.40-7.50 (m, 4H, aryl H); ^{13}C nmr (deuteriochloroform): δ, ppm 23.4 (C-4), 35.1 (C-3), 46.6 (C-5), 116.4 (CN), 118.8, 121.6, 132.1, 137.2 (C aryl), 164.9 (C-2); ms: m/z 265 [M+H]$^+$. *Anal.* Calcd. for $C_{11}H_9BrN_2O$ (MW 265.1): C, 49.84; H, 3.42; N, 10.57. Found: C, 49.87; H, 3.40; N, 10.53.

General Procedure for the Preparation of 5. A solution of **2** (0.92 g, 10 mmoles) and the arylamine (20 mmoles) in ethanol (5 ml) was refluxed for 2 hours (in the case of aniline, 4-methylaniline and 4-methoxyaniline) or 4 hours (4-chloroaniline and 4-bromoaniline). After removal of the solvent *in vacuo*, the residue was purified by column chromatography on silica gel with dichloromethane-acetone (4:1) as the eluent to give **5**.

2-Imino-1-phenyl-3-pyrrolidinecarbonitrile (**5a**). This compound was obtained as pale yellow prisms (1.07 g, 58%), mp 91-92° (acetone-petroleum ether); ir (potassium bromide): ν 3435, 3347, 3200 (NH), 2149 cm^{-1} (CN); ^{1}H nmr (deuteriochloroform): δ, ppm 2.35-2.60 (m, 1H, 4-H), 2.70-2.80 (m, 1H, 4-H), 3.70-3.90 (m, 2.5H, 3-H, 5-H), 4.57 (br. s, 1H, NH_2), 7.10-7.20 (m, 2H, aryl H), 7.30-7.50 (m, 3.5H, NH, aryl H); ms: m/z 186 [M+H]$^+$. *Anal.* Calcd. for $C_{11}H_{11}N_3$ (MW 185.2): C, 71.33; H, 5.99; N, 22.69. Found: C, 71.35; H, 6.06; N, 22.71.

2-Imino-1-(4-methylphenyl)-3-pyrrolidinecarbonitrile (**5b**). This compound was obtained as colorless prisms (1.02 g, 51%), mp 129-130° (acetone-petroleum ether); ir (potassium bromide): ν 3423, 3334, 3240 (NH), 2156 cm^{-1} (CN); ^{1}H nmr (deuteriochloroform): δ, ppm 2.34 (s, 3H, CH_3), 2.40-2.80 (m, 2H, 4-H), 3.75-3.90 (m, 2.6H, 3-H, 5-H), 4.42 (br. s, 0.8H, NH_2), 7.00-7.40 (m, 4.6H, NH, aryl H); ms: m/z 200 [M+H]$^+$. *Anal.* Calcd. for $C_{12}H_{13}N_3$ (MW 199.3): C, 72.33; H, 6.58; N, 21.09. Found: C, 72.52; H, 6.60; N, 21.02.

2-Imino-1-(4-methoxyphenyl)-3-pyrrolidinecarbonitrile (**5c**). This compound was obtained as pale yellow columns (1.32 g, 61%), mp 149-151° (acetone-diethyl ether); ir (potassium bromide): ν 3441, 3275, 3210, 3165 (NH), 2158 cm^{-1} (CN); ^{1}H nmr (deuteriochloroform): δ, ppm 2.35-2.80 (m, 2H, 4-H), 3.81 (s, 3H, CH_3), 3.70-3.90 (m, 2.5H, 3-H, 5-H), 4.48 (br. s, 1H, NH_2), 6.90-7.35 (m, 4.5H, NH, aryl H); ms: m/z 216 [M+H]$^+$. *Anal.* Calcd. for $C_{12}H_{13}N_3O$ (MW 215.3): C, 66.96; H, 6.09; N, 19.52. Found: C, 66.94; H, 6.12; N, 19.57.

1-(4-Chlorophenyl)-2-imino-3-pyrrolidinecarbonitrile (**5d**). This compound was obtained as pale yellow prisms (0.60 g, 27%), mp 127-129° (acetone-petroleum ether); ir (potassium

bromide): ν 3422, 3330, 3237 (NH), 2157 cm^{-1} (CN); ^1H nmr (deuteriochloroform): δ, ppm 2.35-2.60 (m, 1.6H, 4-H), 2.70-2.80 (m, 0.4H, 4-H), 3.75-3.90 (m, 2.8H, 3-H, 5-H), 4.49 (br.s, 0.4H, NH_2), 7.00-7.50 (m, 4.8H, NH, aryl H); ms: m/z 220 $[M+H]^+$. *Anal.* Calcd. for $C_{11}H_{10}ClN_3$ (MW 219.7): C, 60.14; H, 4.59; N, 19.13. Found: C, 60.20; H, 4.65; N, 19.09.

1-(4-Bromophenyl)-2-imino-3-pyrrolidinecarbonitrile (**5e**). This compound was obtained as pale yellow columns (0.62 g, 23%), mp 157-158° (acetone-petroleum ether); ir (potassium bromide):ν 3420, 3330, 3240 (NH), 2158 cm^{-1} (CN); ^1H nmr (deuteriochloroform): δ, ppm 2.35-2.60 (m, 1.4H, 4-H), 2.70-2.80 (m, 0.6H, 4-H), 3.75-3.90 (m, 2.7H, 3-H, 5-H), 4.42 (br. s, 0.6H, NH_2), 7.05-7.55 (m, 4.7H, NH, aryl H); ms: m/z 264 $[M+H]^+$. *Anal.* Calcd. for $C_{11}H_{10}BrN_3$ (MW 264.1): C, 50.02; H, 3.82; N, 15.91. Found: C, 49.99; H, 3.83; N, 15.78.

REFERENCES

[1] P. D. Pohlhaus and J. S. Johnson, *J. Org. Chem.*, **70**, 1057 (2005).

[2] M. E. Alonso and A. Morales, *J. Org. Chem.*, **45**, 4530 (1980).

[3a] R. K. Singh and S. Danishefsky, *J. Org. Chem.*, **41**, 1668 (1975); [b] S. Danishefsky and R. K. Singh, *J. Am. Chem.* Soc., **97**, 3239 (1975).

[4] R. –Y. Zhang and C. –G. Zhao, *Chem. Commun.*, 511 (1996).

[5] S. Husbands, W. Fraser, C. J. Suckling and H. C. S. Wood, *Tetrahedron*, **51**, 865 (1995).

[6] D. Jacoby, J. P. Celerier, G. Haviari, H. Petit ahd G. Lhommet, *Synthesis*, 884 (1992).

[7] J. P. Celerier, M. Haddad, D. Jacoby and G. Lhommet, *Tetrahedron*, *Lett.*, **28**, 6597 (1987).

[8] J. M. Stewart and G. K. Pagenkopf, *J. Org. Chem.*, **34**, 7 (1969).

[9a] K. Yamagata, F. Okabe, H. Maruoka and Y. Tagawa, *J. Heterocyclic Chem.,* **42**, 543 (2005); [b] K. Yamagata, H. Maruoka, Y. Hashimoto and M. Yamazaki, *Heterocycles,* **29**, 5 (1989).

[10] D. A. White, *Synth. Commun.*, **7**, 559 (1977).

[11] J. M. Stewart and H. H. Westberg, *J. Org. Chem.,* **30**, 1951 (1965).