Synthesis of *N*,*N*-Disubstituted 1-Cyanocyclopropanecarboxamides

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2-(Disubstituted amino)-4,5-dihydro-3-furancarbonitriles **1a–i** reacted with acetyl chloride to yield the corresponding ring-opening products **2a–i**. The cyclization of compounds **2a–f** with bases gave the corresponding *N*,*N*-disubstituted 1-cyanocyclopropanecarboxamides **3a–c** and (*E*)-1-cyano-2-phenylcyclopropanecarboxamides **3d–f**. The same compounds **3d–f** were also obtained by treatment of compounds **2g–i** with sodium methoxide.

Introduction

Cyclopropane derivatives have been recognized as an important class of compounds found in natural and synthetic substances, with particularly significant applications in medicinal and agricultural chemistry.[1,2] Hence, the synthetic organic chemistry of cyclopropane-containing compounds has been extensively explored.[3] Ring cleavage by nucleophiles of cyclopropanes substituted at the same ring carbon by two electron-withdrawing groups has been known and studied in a variety of systems.[4,5] Photolysis[6−10] or thermolysis[11−13] of dihydrofurans is known to produce cyclopropanes having one or two electron-withdrawing substituents. However, these methods have unsatisfactory yields, and this disadvantage has prompted us to develop a more efficient method. In the course of our studies on heterocyclic enamino nitriles, we showed that 2-amino-4,5-dihydro-3-furancarbonitrile reacts with sodium iodide to give 1-cyanocyclopropanecarboxamide.[14] Under the same conditions, in the case of 2-(disubstituted amino)-4,5-dihydro-3-furancarbonitriles **1**, a ring-contraction reaction did not take place. Acetyl halides have been used as reagents for the cleavage of cyclic ethers.[16−18] For example, acetyl chloride converts tetrahydrofuran to 4-chlorobutyl acetate. In a previous paper we reported that *N*-benzoyl-4-chloro-2-cyanobutanamides, when refluxed with potassium carbonate in acetone, cyclize to cyclopropanes.[19] These findings suggest the possibility that when compounds **1** are treated with acetyl chloride and base successively, the ring-opening products initially formed may undergo cyclization to furnish cyclopropane derivatives.

Hence, we examined the reaction of compounds **1** with acetyl chloride and then with base.

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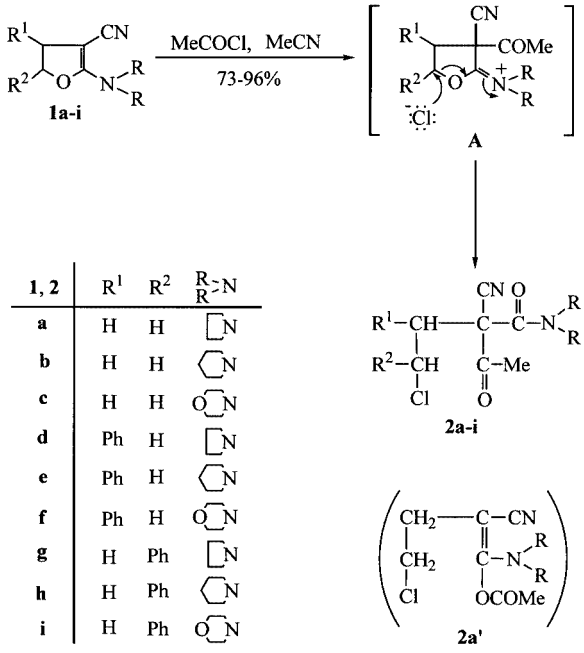
Results and Discussion

When a mixture of 2-pyrrolidin-1-yl-4,5-dihydrofuran-3-carbonitrile (**1a**) and acetyl chloride in acetonitrile was stirred at room temperature, the ring-opening product, 1-(2-acetyl-4-chloro-2-cyanobutanoyl)pyrrolidine (**2a**), was obtained in 96% yield, and no formation of 4-chloro-2-cyano-1-pyrrolidinyl-1-butenyl acetate (**2a′**) was observed (Scheme 1). The IR spectrum of **2a** reveals a band at 2240 cm^{-1} due to a nonconjugated cyano group and two bands at 1730 and 1660 cm^{-1} attributable to the acetyl and the pyrrolidinylcarbonyl groups. The ^{13}C NMR spectrum exhibits a quaternary carbon atom signal at $\delta = 60.0$ ppm and the signals due to olefinic carbon atoms are not observed.



1, 2	R^1	R^2	$\overset{R}{R}$>N
a	H	H	N
b	H	H	N
c	H	H	O N
d	Ph	H	N
e	Ph	H	N
f	Ph	H	O N
g	H	Ph	N
h	H	Ph	N
i	H	Ph	O N

Scheme 1. Reaction of 2-(disubstituted amino)-4,5-dihydro-3-furancarbonitriles **1a−i** with acetyl chloride

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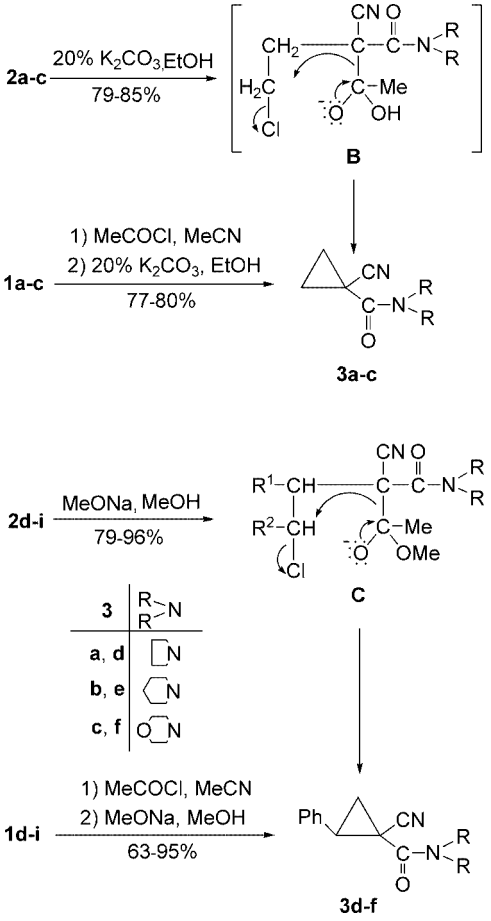
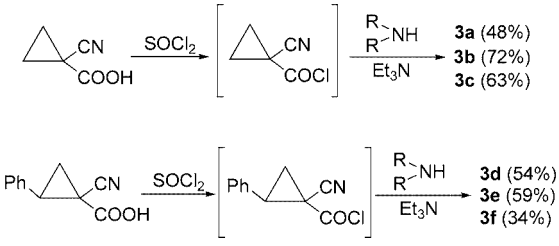
The carbon signal at δ = 60.0 ppm has been assigned to the C-2 carbon atom bearing acetyl and pyrrolidinylcarbonyl groups. These spectroscopic data are consistent with 1-butanoylpyrrolidine **2a** rather than 1-butenyl acetate **2a′**. Compounds **1b**−**i** react with acetyl chloride under the same conditions to afford the corresponding 2-acetyl-4-chlorobutanenitriles **2b**−**i** in good to excellent yields. All nine ring-opening products **2a**−**i** are relatively unstable, so crystalline compounds **2c**−**i** are partially decomposed during recrystallization.

Subsequently, in order to obtain the cyclopropane derivatives, we examined the cyclization of compounds **2a**−**i** with bases. The reactions of **2a**−**c** with aqueous potassium carbonate resulted in the formation of the expected cyclopropanes **3a**−**c** in good yields (Scheme 2). Compounds **2d**−**f** were easily cyclized to the cyclopropane derivatives **3d**−**f** when treated with sodium methoxide. The same compounds **3d**−**f** were also obtained by treatment of **2g**−**i** with sodium methoxide. The structures of **3a**−**f** were confirmed by direct comparison with authentic samples, which were synthesized by the following methods (Scheme 3): Conversion of 1-cyanocyclopropanecarboxylic acid [20] or (*E*)-1-cyano-2-phenylcyclopropanecarboxylic acid [21] with thionyl chloride provided cyclopropanecarbonyl chlorides, and subsequent treatment with amines gave 1-cyanocyclopropanecarboxamides **3a**−**c** or (*E*)-1-cyano-2-phenylcyclopropanecarboxamides **3d**−**f** in 34−72% yields. Thus, compounds **3d**−**f** have the (*E*) configuration.



Scheme 2. Synthesis of *N*, *N*-disubstituted 1-cyanocyclopropanecarboxamides **3a**−**f**



Scheme 3. Synthesis of **3a**−**f** from 1-cyanocyclopropanecarboxylic acid and (*E*)-1-cyano-2-phenylcyclopropanecarboxylic acid

The formation of **3** can be rationalized by the mechanism shown in Schemes 1 and Scheme 2. Acetyl chloride attacks at the 3-position of **1** to form the intermediate iminium salts **A**, which undergo ring opening between the oxygen atom and the C-5 position of **A** by a chloride ion to produce **2**. The hydroxide or the methoxide ion attacks the carbonyl carbon atom of the acetyl group of **2** to form the alkoxide **B/C**, which then is cyclized to **3**.

Finally, we investigated a one-pot synthesis of **3** by a ring-cleavage/cyclization process. The typical procedure was as follows: Acetyl chloride was added to a suspension of **1d**−**f** in acetonitrile at room temperature. After the starting materials **1d**−**f** had disappeared, the solvent was removed, and sodium methoxide in methanol was added to the residue. The mixture was stirred at room temperature for 1 h to give **3d**,**e**,**f** in 94, 94, and 93% yields, respectively. Similar reactions of **1g**−**i** gave **3g**−**i** in good yields. Successive treatment of **1a**,**b**,**c** with acetyl chloride and aqueous potassium carbonate resulted in the formation of **3a**,**b**,**c** in 77, 80, and 77% yields, respectively.

In conclusion, from a viewpoint of simple operation, mild conditions, and good yields in the preparation of 2-acetyl-4-chlorobutanenitriles as well as in the cyclization step, the present reactions provide a useful method for the synthesis of *N*,*N*-disubstituted 1-cyanocyclopropanecarboxamides.

Experimental Section

General: All melting points are uncorrected. IR spectra were taken with a Jasco A-302 spectrometer. ^{1}H 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) in $CDCl_3$ with TMS as internal standard. ^{13}C signal assignments were confirmed by the DEPT technique. Mass spectra were recorded with a Jeol JMS-HX110 instrument at 70 eV. Elemental analyses were performed using an MT-6 elemental analyzer (Yanaco). The starting compounds **1a**−**i** were prepared as previously described.[15,22]

General Procedures for the Synthesis of 2-Acetyl-4-chloro-2-cyanobutanamides 2. Procedure A: Acetyl chloride (1.73 g, 22 mmol) was added to an ice-cooled and stirred solution of **1a**−**c** (20 mmol) in acetonitrile (20 mL). The mixture was stirred at room temperature

for 4 h. After removal of the solvent in vacuo, the residue was chromatographed on silica gel with CH_2Cl_2 as the eluent to give **2a**−**c**. **Procedure B:** A suspension of **1d**−**i** (20 mmol) and acetyl chloride (1.73 g, 22 mmol) in acetonitrile (20 mL) was stirred at room temperature for 4 h (in the case of the preparation of **2d**,**e**,**g**−**i**) or 20 h (**2f**). The solvent was removed and diisopropyl ether (30 mL) was added to the residue. The precipitate was collected and washed with diisopropyl ether.

1-(2-Acetyl-4-chloro-2-cyanobutanoyl)pyrrolidine (2a): Yield 4.64 g (96%). Colorless oil. IR (neat): $\tilde{\nu}$ = 2240 [ν(C≡N)], 1730 [ν(C=O)], 1660 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.86−2.08 (m, 4 H, NCH_2CH_2), 2.35 (s, 3 H, CH_3), 2.53 (ddd, *J* = 6.4, 9.2, 14.2 Hz, 1 H, 3-H), 2.74 (ddd, *J* = 5.5, 9.2, 14.2 Hz, 1 H, 3-H), 3.32−3.58 (m, 4 H, NCH_2), 3.63 (ddd, *J* = 6.4, 9.2, 11.0 Hz, 1 H, 4-H), 3.77 (ddd, *J* = 5.5, 9.2, 11.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR: δ = 23.5 (CH_2), 25.8 (CH_3), 26.6 (CH_2), 36.3 (C-3), 39.4 (C-4), 47.5 (NCH_2), 48.4 (NCH_2), 60.0 (C-2), 115.2 (C≡N), 159.2 (C=O), 195.0 (C=O) ppm. MS (FAB): *m*/*z* (%) = 243 (100) [M^+ + H]. $C_{11}H_{15}ClN_2O_2$ (242.7): calcd. C 54.44, H 6.23, N 11.54; found C 54.60, H 6.26, N 11.70.

1-(2-Acetyl-4-chloro-2-cyanobutanoyl)piperidine (2b): Yield 4.70 g (92%). Pale yellow oil. IR (neat): $\tilde{\nu}$ = 2250 [ν(C≡N)], 1730 [ν(C=O)], 1660 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.50−1.75 (m, 6 H, $NCH_2CH_2CH_2CH_2$), 2.36 (s, 3 H, CH_3), 2.52 (ddd, *J* = 6.1, 9.5, 14.1 Hz, 1 H, 3-H), 2.73 (ddd, *J* = 5.2, 9.5, 14.1 Hz, 1 H, 3-H), 3.35−3.58 (m, 4 H, NCH_2), 3.62 (ddd, *J* = 6.1, 9.5, 11.3 Hz, 1 H, 4-H), 3.77 (ddd, *J* = 5.2, 9.5, 11.3 Hz, 1 H, 4-H) ppm. ^{13}C NMR: δ = 24.1 (CH_2), 25.3 (CH_2), 25.7 (CH_3), 36.7 (C-3), 39.4 (C-4), 45.2 (NCH_2), 47.6 (NCH_2), 59.1 (C-2), 115.5 (C≡N), 159.8 (C=O), 195.5 (C=O) ppm. MS (FAB): *m*/*z* (%) = 257 (100) [M^+ + H]. $C_{12}H_{17}ClN_2O_2$ (256.7): calcd. C 56.14, H 6.67, N 10.91; found C 56.32, H 6.73, N 11.03.

1-(2-Acetyl-4-chloro-2-cyanobutanoyl)morpholine (2c): Yield 4.50 g (87%). M.p. 66−67 °C. Colorless prisms (diethyl ether/petroleum ether). IR (KBr): $\tilde{\nu}$ = 2260 [ν(C≡N)], 1725 [ν(C=O)], 1660 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 2.38 (s, 3 H, CH_3), 2.55 (ddd, *J* = 6.4, 9.2, 14.4 Hz, 1 H, 3-H), 2.75 (ddd, *J* = 5.5, 9.2, 14.4 Hz, 1 H, 3-H), 3.40−3.80 (m, 10 H, 4-H, NCH_2CH_2O) ppm. ^{13}C NMR: δ = 25.7 (CH_3), 36.6 (C-3), 39.2 (C-4), 44.2 (NCH_2), 47.2 (NCH_2), 59.1 (C-2), 66.0 (OCH_2), 66.3 (OCH_2), 115.2 (C≡N), 160.2 (C=O), 195.3 (C=O) ppm. MS (FAB): *m*/*z* (%) = 259 (89) [M^+ + H]. $C_{11}H_{15}ClN_2O_3$ (258.7): calcd. C 51.07, H 5.84, N 10.83; found C 51.02, H 5.83, N 10.81.

1-(2-Acetyl-4-chloro-2-cyano-3-phenylbutanoyl)pyrrolidine (2d): Yield 4.63 g (73%). M.p. 141 °C (dec.). Colorless prisms (acetone/petroleum ether). IR (KBr): $\tilde{\nu}$ = 2260 [ν(C≡N)], 1725 [ν(C=O)], 1660 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.80−2.10 (m, 4 H, NCH_2CH_2), 1.88 (s, 3 H, CH_3), 3.10−3.20 (m, 1 H, NCH_2), 3.55−3.80 (m, 3 H, NCH_2), 3.94 (t, *J* = 10.4 Hz, 3-H), 4.15 (dd, *J* = 3.7, 10.4 Hz, 4-H), 4.20 (dd, *J* = 3.7, 10.4 Hz, 4-H), 7.30−7.40 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 23.4 (CH_3), 26.6 (CH_2), 27.0 (CH_2), 45.3 (C-4), 47.4 (NCH_2), 48.7 (NCH_2), 50.9 (C-3), 65.0 (C-2), 115.4 (C≡N), 129.0, 129.1, 129.3, 134.4 (C aryl), 158.8 (C=O), 194.9 (C=O) ppm. MS (FAB): *m*/*z* (%) = 319 (75) [M^+ + H]. $C_{17}H_{19}ClN_2O_2$ (318.8): calcd. C 64.05, H 6.01, N 8.79; found C 64.00, H 6.02, N8.76.

1-(2-Acetyl-4-chloro-2-cyano-3-phenylbutanoyl)piperidine (2e): Yield 4.94 g (74%). M.p. 136 °C (dec.). Colorless prisms (diethyl ether). IR (KBr): $\tilde{\nu}$ = 2240 [ν(C≡N)], 1730 [ν(C=O)], 1640 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.30−1.75 (m, 6 H, $NCH_2CH_2CH_2CH_2$), 1.83 (s, 3 H, CH_3), 3.20−3.70 (m, 4 H, NCH_2), 3.95 (t, *J* = 11.6 Hz, 1 H, 3-H), 4.13−4.19 (m, 2 H, 4-H), 7.30−7.40 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 24.1 (CH_3), 25.2 (CH_2), 26.6 (CH_2), 45.6 (C-4), 47.5 (NCH_2), 51.3 (C-3), 63.8 (C-2), 115.8 (C≡N), 128.9, 129.1, 129.4, 134.3 (C aryl), 159.6 (C=O), 195.2 (C=O) ppm. MS (FAB): *m*/*z* (%) = 333 (63) [M^+ + H]. $C_{18}H_{21}ClN_2O_2$ (332.8): calcd. C 64.96, H 6.36, N 8.42; found C 64.97, H 6.42, N 8.48.

1-(2-Acetyl-4-chloro-2-cyano-3-phenylbutanoyl)morpholine (2f): Yield 5.43 g (81%). M.p. 174 °C (dec.). Colorless prisms (acetone/petroleum ether). IR (KBr): $\tilde{\nu}$ = 2240 [ν(C≡N)], 1730 [ν(C=O)], 1660 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.85 (s, 3 H, CH_3), 3.50−3.80 (m, 8 H, NCH_2CH_2O) 3.95 (t, *J* = 10.7 Hz, 1 H, 3-H), 4.12 (dd, *J* = 3.6, 10.7 Hz, 1 H, 4-H), 4.18 (dd, *J* = 3.6, 10.7 Hz, 1 H, 4-H), 7.37−7.40 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 26.6 (CH_3), 44.6 (NCH_2), 45.4 (C-4), 47.0 (NCH_2) 51.1 (C-3), 63.9 (C-2), 65.7 (OCH_2), 66.3 (OCH_2), 115.5 (C≡N), 129.1, 129.2, 129.3, 134.0 (C aryl) 160.1 (C=O), 195.0 (C=O) ppm. MS (FAB): *m*/*z* (%) = 335 (64) [M^+ + H]. $C_{17}H_{19}ClN_2O_3$ (334.8): calcd. C 60.99, H 5.72, N 8.37; found C 61.04, H 5.67, N 8.53.

1-(2-Acetyl-4-chloro-2-cyano-4-phenylbutanoyl)pyrrolidine (2g): Yield 5.31 g (83%). M.p. 108−110 °C. Colorless prisms (acetone/petroleum ether). IR (KBr): $\tilde{\nu}$ = 2260 [ν(C≡N)], 1730 [ν(C=O)], 1670 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.80−2.00 (m, 4 H, NCH_2CH_2), 2.18 (s, 3 H, CH_3), 2.94 (dd, *J* = 6.8, 15.0 Hz, 1 H, 3-H), 3.13 (dd, *J* = 6.8, 15.0 Hz, 1 H, 3-H), 3.40−3.75 (m, 4 H, NCH_2), 5.18 (t, *J* = 6.8 Hz, 1 H, 4-H), 7.30−7.45 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 23.3 (CH_3), 26.1 (CH_2), 26.6 (CH_2), 43.1 (C-3), 47.6 (NCH_2), 48.5 (NCH_2), 58.8(C-4), 59.5 (C-2), 115.5 (C≡N), 127.4, 128.8, 129.0, 140.0 (C aryl), 159.7 (C=O), 194.7 (C=O) ppm. MS (FAB): *m*/*z* (%) = 319 (45) [M^+ + H]. $C_{17}H_{19}ClN_2O_2$ (318.8): calcd. C 64.05, H 6.01, N 8.79; found C 63.95, H 6.09, N 8.82.

1-(2-Acetyl-4-chloro-2-cyano-4-phenylbutanoyl)piperidine (2h): Yield 5.04 g (76%). M.p. 86−87 °C. Colorless prisms (diethyl ether/petroleum ether). IR (KBr): $\tilde{\nu}$ = 2250 [ν(C≡N)], 1725 [ν(C=O)], 1660 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.50−1.70 (m, 6 H, $NCH_2CH_2CH_2CH_2$), 2.17 (s, 3 H, CH_3), 3.00 (dd, *J* = 6.7, 15.0 Hz, 1 H, 3-H), 3.06 (dd, *J* = 6.7, 15.0 Hz, 1 H, 3-H), 3.40−3.60 (m, 4 H, NCH_2), 5.17 (t, *J* = 6.7 Hz, 1 H, 4-H), 7.30−7.45 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 24.1 (CH_3), 25.2 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 43.8 (C-3), 45.2 (NCH_2), 47.7 (NCH_2), 58.6 (C-2), 58.7 (C-4), 115.8 (C≡N), 127.5, 128.8, 129.0, 140.1 (C aryl), 160.3 (C=O), 195.3 (C=O) ppm. MS (FAB): *m*/*z* (%) = 333 (20) [M^+ + H]. $C_{18}H_{21}ClN_2O_2$ (332.8): calcd. C 64.96, H 6.36, N 8.42; found C 65.05, H 6.31, N 8.44.

1-(2-Acetyl-4-chloro-2-cyano-4-phenylbutanoyl)morpholine (2i): Yield 5.22 g (78%). M.p. 121−122 °C. Colorless prisms (acetone/petroleum ether). IR (KBr): $\tilde{\nu}$ = 2240 [ν(C≡N)], 1730 [ν(C=O)], 1670 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 2.19 (s, 3 H, CH_3), 2.99 (dd, *J* = 6.7, 15.0 Hz, 1 H, 3-H), 3.08 (dd, *J* = 6.7, 15.0 Hz, 1 H, 3-H), 3.40−3.75 (m, 8 H, NCH_2CH_2O), 5.16 (t, *J* = 6.7 Hz, 1 H, 4-H), 7.30−7.45 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 26.1 (CH_3), 43.7 (C-3), 44.6 (NCH_2), 47.0 (NCH_2), 58.5 (C-4), 58.7 (C-2), 63.8 (OCH_2), 66.1 (OCH_2), 115.6 (C≡N), 127.4, 128.9, 129.2, 139.9 (C aryl), 160.7 (C=O), 195.1 (C=O) ppm. MS (FAB): *m*/*z* (%) = 335 (44) [M^+ + H]. $C_{17}H_{19}ClN_2O_3$ (334.8): calcd. C 60.99, H 5.72, N 8.37; found C 60.91, H 5.72, N 8.37.

General Procedures for the Synthesis of 1-Cyanocyclopropanecarboxamides 3. Procedure A: A mixture of **2a**−**c** (5 mmol), 20% K_2CO_3 (10 mL), and EtOH (10 mL) was stirred at room temperature for 2 h. The solvent was removed and H_2O (20 mL) was added to the residue. The mixture was extracted with EtOAc. The extract

was washed with H_2O, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with CH_2Cl_2/acetone (4:1) as the eluent to yield **3a** (0.68 g, 83%), **3b** (0.76 g, 85%), and **3c** (0.71 g, 79%). **Procedure B:** A mixture of **2d**−**i** (5 mmol) and MeONa (0.30 g, 5.5 mmol) in MeOH (15 mL) was stirred at room temperature for 1 h. After removal of the MeOH in vacuo, H_2O (20 mL) was added to the residue and the mixture was extracted with EtOAc. The extract was washed with H_2O, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2/acetone (4:1) as the eluent to give **3d** [from **2d**: 1.14 g (95%); from **2g**: 1.15 g (96%)], **3e** [from **2e**: 1.12 g (96%); from **2h:** 1.20 g (94%)], **3f** [from **2f**: 1.16 g (91%); from **2i**: 1.01 g (79%)]. **Procedure C:** A mixture of **1a**−**c** (20 mmol) and acetyl chloride (1.73 g, 22 mmol) in acetonitrile (20 mL) was stirred at room temperature for 4 h. After removal of the solvent in vacuo, 20% K_2CO_3 (25 mL) and EtOH (25 mL) were added to the residue. The resulting mixture was stirred at room temperature for 2 h. The solvent was removed and H_2O (40 mL) was added to the residue. The mixture was extracted with EtOAc. The extract was washed with H_2O, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with CH_2Cl_2/acetone (4:1) as the eluent to afford **3a** (2.51 g, 77%), **3b** (2.83 g, 80%), and **3c** (2.76 g, 77%). **Procedure D:** A mixture of **1d**−**i** (20 mmol) and acetyl chloride (1.73 g, 22 mmol) in acetonitrile (20 mL) was stirred at room temperature for 4 h (in the case of the reaction of **1d**,**e**,**g**−**i**) or 20 h (**1f**). After removal of the solvent in vacuo, MeONa (1.19 g, 22 mmol) in MeOH (30 mL) was added to the residue. The resulting mixture was stirred at room temperature for 1 h. The solvent was removed and H_2O (40 mL) was added to the residue. The mixture was extracted with EtOAc. The extract was washed with H_2O, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2/acetone (4:1) as the eluent to give **3d** [from **1d**: 4.60 g (94%); from **1g**: 4.61 g (94%)], **3e** [from **1e**: 4.76 g (94%); from **1h** 4.82 g (95%)], and **3f** [from **1f**: 4.78 g (93%); from **1i**: 3.23 g (63%)]. **Procedure E:** A mixture of 1-cyanocyclopropanecarboxylic acid (0.56 g, 5 mmol) or (*E*)-1-cyano-2-phenylcyclopropanecarboxylic acid (0.94 g, 5 mmol) and $SOCl_2$ (3 mL) was refluxed for 1 h. After removal of the $SOCl_2$ under reduced pressure, a solution of pyrrolidine (0.71 g, 10 mmol) [piperidine (0.85 g, 10 mmol) or morpholine (0.87 g, 10 mmol)] and triethylamine (1.01 g, 10 mmol) in THF (10 mL) was added to the residue. The mixture was stirred at room temperature for 30 min. The solvent was removed and H_2O (20 mL) was added to the residue. The mixture was extracted with EtOAc. The extract was washed with H_2O, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel with CH_2Cl_2 as the eluent to give **3a** (0.39 g, 48%), **3b** (0.64 g, 72%), **3c** (0.57 g, 63%), **3d** (0.65 g, 54%), **3e** (0.75 g, 59%), and **3f** (0.43 g, 34%).

1-[(1-Cyanocyclopropyl)carbonyl]pyrrolidine (3a): M.p. 51−52 °C. Colorless columns (diethyl ether/petroleum ether). IR (KBr): $\tilde{\nu}$ = 2260 [ν(C≡N)], 1640 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.47−1.50 (m, 2 H, CH_2), 1.64−1.70 (m, 2 H, CH_2), 1.88−1.93 (m, 2 H, NCH$_2$CH_2), 1.99−2.03 (m, 2 H, NCH$_2$CH_2), 3.47−3.50 (m, 2 H, NCH_2CH$_2$), 3.84−3.90 (m, 2 H, NCH_2CH$_2$) ppm. ^{13}C NMR: δ = 13.5 (C-1), 16.6 (*C*H$_2$), 24.0 (*C*H$_2$), 26.4 (*C*H$_2$), 47.5 (N*C*H$_2$), 47.6 (N*C*H$_2$), 120.2 (C≡N), 162.6 (C=O) ppm. MS (FAB): *m*/*z* (%) = 165 (100) [M^+ + H]. $C_9H_{12}N_2O$ (164.2): calcd. C 65.83, H 7.37, N 17.06; found C 65.80, H 7.46, N 17.06.

1-[(1-Cyanocyclopropyl)carbonyl]piperidine (3b): M.p. 91−92 °C. Colorless columns (diethyl ether/petroleum ether). IR (KBr): $\tilde{\nu}$ = 2240 [ν(C≡N)], 1640 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.46−1.58 (m, 4 H, CH_2), 1.50−1.75 (m, 6 H, NCH_2CH_2CH_2CH_2), 3.40−3.80 (m, 4 H, NCH_2) ppm. ^{13}C NMR: δ = 13.1 (C-1), 15.4 (*C*H$_2$), 24.4 (*C*H$_2$), 25.5 (*C*H$_2$), 44.6 (N*C*H$_2$), 47.5 (N*C*H$_2$), 120.2 (C≡N), 162.9 (C=O) ppm. MS (FAB): *m*/*z* (%) = 179 (100) [M^+ + H]. $C_{10}H_{14}N_2O$ (178.2): calcd. C 67.39, H 7.92, N 15.72; found C 67.22, H 7.87, N 15.62.

1-[(1-Cyanocyclopropyl)carbonyl]morpholine (3c): M.p. 84−85 °C. Colorless columns (diethyl ether). IR (KBr): $\tilde{\nu}$ = 2240 [ν(C≡N)], 1645 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.51−1.54 (m, 2 H, CH_2), 1.59−1.62 (m, 2 H, CH_2), 3.50−3.90 (m, 8 H, NCH_2CH_2O) ppm. ^{13}C NMR: δ = 12.8 (C-1), 15.6 (*C*H$_2$), 43.7 (N*C*H$_2$), 46.8 (N*C*H$_2$), 66.4 (O*C*H$_2$), 119.9 (C≡N), 163.4 (C=O) ppm. MS (FAB): *m*/*z* (%) = 181 (100) [M^+ + H]. $C_9H_{12}N_2O_2$ (180.2): calcd. C 59.98, H 6.71, N 15.55; found C 59.79, H 6.68, N 15.52.

(*E*)-1-[(1-Cyano-2-phenylcyclopropyl)carbonyl]pyrrolidine (3d): Colorless oil. IR (neat): $\tilde{\nu}$ = 2240 [ν(C≡N)], 1650 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.90−2.03 (m, 5 H, 3-H, NCH$_2$CH_2), 2.24 (dd, *J* = 5.5, 8.6 Hz, 1 H, 3-H), 3.02 (t, *J* = 8.6 Hz, 1 H, 2-H), 3.50−3.55 (m, 2 H, NCH_2CH$_2$), 3.70−3.85 (m, 2 H, NCH_2CH$_2$), 7.28−7.40 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 20.4 (C-3), 23.6 (C-1), 24.0 (*C*H$_2$), 26.5 (*C*H$_2$), 33.0 (C-2), 47.6 (N*C*H$_2$), 47.8 (N*C*H$_2$), 117.8 (C≡N), 128.1, 128.7, 133.9 (C aryl), 162.5 (C=O) ppm. MS (FAB): *m*/*z* (%) = 241 (100) [M^+ + H]. $C_{15}H_{16}N_2 \cdot 0.2H_2O$ (243.9): calcd. C 73.87, H 6.78, N 11.49; found C 73.89, H 6.76, N 11.51.

(*E*)-1-[(1-Cyano-2-phenylcyclopropyl)carbonyl]piperidine (3e): Colorless oil. IR (neat): $\tilde{\nu}$ = 2250 [ν(C≡N)], 1660 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 1.60−1.70 (m, 6 H, NCH$_2$CH_2CH_2CH_2), 1.96 (dd, *J* = 5.8, 8.5 Hz, 1 H, 3-H), 2.21 (t, *J* = 5.8, 8.5 Hz, 1 H, 3-H), 2.84 (t, *J* = 8.5 Hz, 1 H, 2-H) 3.50−3.70 (m, 4 H, NCH_2), 7.25−7.40 (m, 5 H, aryl) ppm. ^{13}C NMR: δ = 19.0 (C-3), 23.2 (C-1), 24.4 (*C*H$_2$), 25.8 (*C*H$_2$), 31.9 (C-2), 44.6 (N*C*H$_2$), 47.6 (N*C*H$_2$), 117.7 (C≡N), 127.8, 128.2, 128.8, 133.6 (C aryl), 162.8 (C=O) ppm. MS (FAB): *m*/*z* (%) = 255 (100) [M^+ + H]. $C_{16}H_{18}N_2O$ (254.3): calcd. C 75.56, H 7.13, N 11.01; found C 75.45, H 7.25, N 10.92.

(*E*)-1-[(1-Cyano-2-phenylcyclopropyl)carbonyl]morpholine (3f): M.p. 91−92 °C. Colorless needles (diethyl ether/petroleum ether). IR (KBr): $\tilde{\nu}$ = 2240 [ν(C≡N)], 1670 [ν(C=O)] cm^{-1}. ^1H NMR: δ = 2.01 (dd, *J* = 5.8, 9.2 Hz, 1 H, 3-H), 2.23 (dd, *J* = 5.8, 9.2 Hz, 1 H, 3-H), 2.89 (t, *J* = 9.2 Hz, 1 H, 2-H), 3.60−3.80 (m, 8 H, NCH$_2$CH_2O), 7.25−7.42 (m, 5 H, aryl) ppm.^{13}C NMR: δ = 19.2 (C-3), 22.9 (C-1), 32.3 (C-2), 44.0 (N*C*H$_2$), 47.0 (N*C*H$_2$), 66.4 (O*C*H$_2$), 117.5 (C≡N), 127.7, 128.4, 128.9, 133.2 (C aryl), 163.3 (C=O) ppm. MS (FAB): *m*/*z* (%) = 257 (100) [M^+ + H]. $C_{15}H_{16}N_2O_2$ (256.3): calcd. C 70.29, H 6.29, N 10.93; found C 70.26, H 6.39, N 10.81.

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