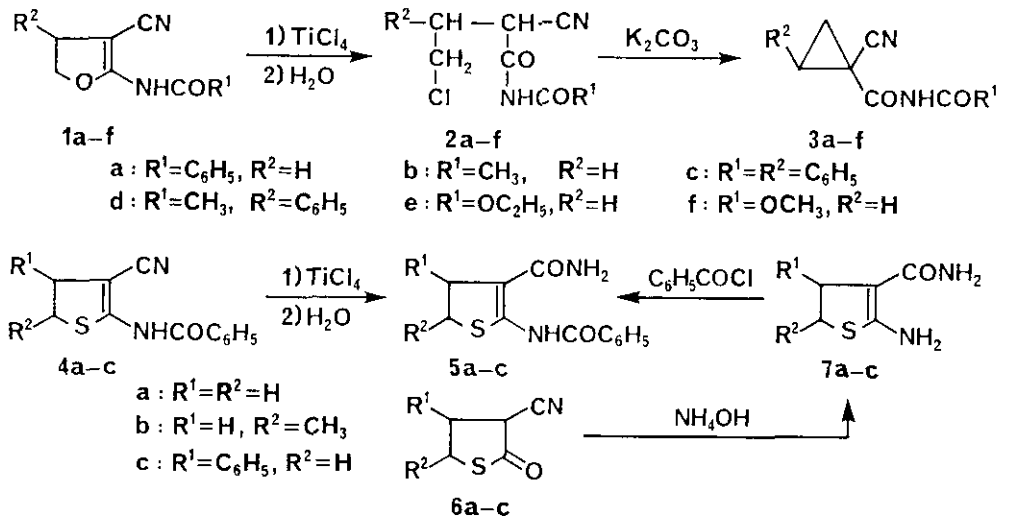
RING OPENING OF 2-ACYLAMINO-4,5-DIHYDRO-3-FURANCARBONITRILES BY USE OF TITANIUM (IV) CHLORIDE[1]

Hiroshi Maruoka, Kenji Yamagata, and Motoyoshi Yamazaki*
Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku, Fukuoka 814-01, Japan

Abstract ——— The ring opening of 2-acylamino-4,5-dihydro-3-furancarbonitriles (**1a-f**) with titanium (IV) chloride gave the corresponding N-acyl-4-chloro-2-cyanobutanamides (**2a-f**). On treatment with potassium carbonate, compounds (**2a-f**) were converted to the corresponding N-acyl-1-cyanocyclopropanecarboxamides (**3a-f**). On the other hand, the reaction of 2-benzamido-4,5-dihydro-3-thiophenecarbonitriles (**4a-c**) with titanium (IV) chloride gave the corresponding 2-benzamido-4,5-dihydro-3-thiophenecarboxamides (**5a-c**).

In the preceding paper,[2] we reported that the reaction of 2-amino-4,5-dihydro-3-furancarbonitriles with a sodium halide gave 1-cyanocyclopropanecarboxamides, and proposed that this reaction occurs via the ring opening of 2-amino-4,5-dihydro-3-furancarbonitriles by a halide ion to give 2-cyano-4-halogenobutanamides, which undergo cyclization to form the cyclopropanecarboxamides. This reaction suggests the possibility that the intermediates, 2-cyano-4-halogenobutanamides may be prepared from 2-amino-4,5-dihydro-3-furancarbonitriles. Attempts to prepare 2-cyano-4-halogenobutanamides were unsuccessful. Therefore, we examined this reaction with 2-benzamido-4,5-dihydro-3-furancarbonitriles[3] instead of 2-amino-4,5-dihydro-3-furancarbonitriles, but the desired products were not obtained. However, we found that when titanium (IV) chloride was used in place of a so-

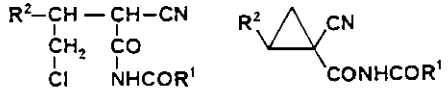
dium halide, the expected products were obtained. We report here a synthesis of N-acyl-4-chloro-2-cyanobutanamides, and also describe their cyclization. When a solution of 2-benzamido-4,5-dihydro-3-furancarbonitrile (**1a**)[3] and titanium (IV) chloride (1.2 eq.) in chloroform was refluxed for 1 h, the expected N-benzoyl-4-chloro-2-cyanobutanamide (**2a**) was obtained in 82% yield. The ir spectrum of **2a** exhibited bands due to a nonconjugated cyano group at 2250 cm^{-1} and carbonyl groups at 1740 and 1695 cm^{-1}. The ^1H nmr spectrum showed a one-proton double doublet at δ 5.00 assignable to a methine group, and a two-proton multiplet at δ 2.17-2.71 and a two-proton triplet at δ 3.76 indicative of two methylene groups, besides the signals due to an imino proton and the aromatic protons.



Scheme 1

Compound (**2a**) reacted with potassium carbonate in refluxing acetone to yield N-benzoyl-1-cyanocyclopropanecarboxamide (**3a**) which was proved to be identical with an authentic sample prepared by the reaction of N-benzoyl-α-cyanoacetamide[4] with 1,2-dibromoethane in the presence of sodium hydride. When **3a** was treated with titanium (IV) chloride in chloroform, **2a**

Table 1. Some Properties of 2a-f and 3a-f



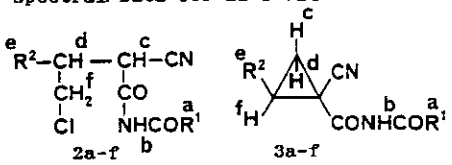
2a-f

3a-f

a : R^1=C_6H_5, R^2=H
b : R^1=CH_3, R^2=H
c : R^1=R^2=C_6H_5
d : R^1=CH_3, R^2=C_6H_5
e : R^1=OC_2H_5, R^2=H
f : R^1=OCH_3, R^2=H

Compd No.	Yield (%)	mp (°C) (Recrystallization solvent)	Appearance (Colorless)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	82	118-119 (acetone-petr.benzin)	Needles	$C_{12}H_{11}N_2O_2Cl$	57.49 (57.59)	4.42 (4.40)	11.18 (11.14)
2b	55	68-69 (CH_2Cl_2-petr.benzin)	Prisms	$C_7H_9N_2O_2Cl$	44.58 (44.33)	4.81 (4.81)	14.85 (14.90)
2c	59	148-149 (CH_2Cl_2-petr.benzin)	Prisms	$C_{18}H_{15}N_2O_2Cl$	66.16 (66.02)	4.63 (4.60)	8.57 (8.36)
2d	54	106-107 (CH_2Cl_2-petr.benzin)	Needles	$C_{13}H_{13}N_2O_2Cl$	58.99 (59.21)	4.95 (5.15)	10.58 (10.43)
2e	87	68-69 (ether-petr.ether)	Prisms	$C_8H_{11}N_2O_3Cl$	43.95 (44.14)	5.07 (5.13)	12.81 (12.72)
2f	85	78-79 (ether-petr.ether)	Prisms	$C_7H_9N_2O_3Cl$	41.09 (41.05)	4.43 (4.51)	13.69 (13.71)
3a	96	125-126 (acetone-petr.benzin)	Needles	$C_{12}H_{10}N_2O_2$	67.28 (67.35)	4.71 (4.60)	13.08 (13.23)
3b	87	92-93 (acetone-petr.benzin)	Columns	$C_7H_8N_2O_2$	55.25 (55.21)	5.30 (5.33)	18.41 (18.49)
3c	97	135-136 (acetone-petr.benzin)	Columns	$C_{18}H_{14}N_2O_2$	74.47 (74.50)	4.86 (4.75)	9.65 (9.70)
3d	81	112-113 (acetone-petr.benzin)	Needles	$C_{13}H_{12}N_2O_2$	68.41 (68.67)	5.30 (5.32)	12.27 (12.23)
3e	92	107-108 (acetone-petr.benzin)	Needles	$C_8H_{10}N_2O_3$	52.74 (52.65)	5.53 (5.49)	15.38 (15.34)
3f	92	96-98 (acetone-petr.benzin)	Needles	$C_7H_8N_2O_3$	50.00 (50.14)	4.80 (4.79)	16.66 (16.87)

Table 2. Spectral Data for 2a-f and 3a-f

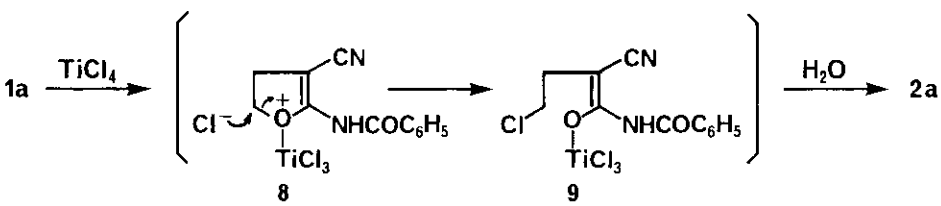


a : R^1=C_6H_5, R^2=H
b : R^1=CH_3, R^2=H
c : R^1=R^2=C_6H_5
d : R^1=CH_3, R^2=C_6H_5
e : R^1=OC_2H_5, R^2=H
f : R^1=OCH_3, R^2=H

Compd No.	ir ν_{max}^{KBr} cm^{-1}			^{1}H nmr spectra (ppm) in $CDCl_3$ solution (J in Hz)					
	NH	CN	CO	H^a	H^b	H^c	H^d	H^e	H^f
2a	3250	2250	1740	7.39-7.71(3H, m)	9.44	5.00	2.17-2.71		3.76
	3170		1695	7.78-7.98(2H, m)	(br s)	(dd, J=8.5, 5.5)	(m)		(t, J=6.0)
2b	3265	2255	1735	2.37(s)	9.12	4.34	2.28-2.56		3.74
	3210		1705		(br s)	(dd, J=8.0, 6.5)	(m)		(t, J=6.0)
2c	3355	2250	1718	7.38-7.64(3H, m)	9.23	5.53	3.68-4.16	7.16-7.32	3.68-4.16
			1690	7.75-7.86(2H, m)	(br s)	(d, J=5.0)	(m)	(m)	(m)
2d	3455	2250	1735	2.27(s)	8.94	4.72	3.60-4.10	7.24-7.86	3.60-4.10
	3165		1705		(br s)	(d, J=5.0)	(m)	(m)	(m)
2e	3270	2250	1765	1.34(3H, t, J=7.0)	8.02	4.73	2.30-2.54		3.74
	3215		1690	4.30(2H, q, J=7.0)	(br s)	(t, J=7.0)	(m)		(t, J=6.0)
2f	3265	2260	1765	3.86(s)	8.08	4.73	2.30-2.54		3.74
	3200		1700		(br s)	(dd, J=8.0, 7.0)	(m)		(t, J=6.5)
3a	3340	2245	1725	7.36-7.67(3H, m)	9.36	1.58-1.92			
			1675	7.76-7.90(2H, m)	(br s)		(m)		
3b	3280	2250	1735	2.45(s)	8.64	1.64-1.81			
			1688		(br s)		(m)		
3c	3430	2230	1755	7.30-7.73(3H, m)	9.43	2.37[a]	2.19[a]	7.30-7.73	3.34
			1692	7.80-7.93(2H, m)	(br s)	(dd, J=9.5, 5.5)	(dd, J=9.0, 5.5)	(m)	(t, J=9.0)
3d	3280	2235	1740	2.48(s)	8.62	2.28[b]	2.17[b]	7.18-7.44	3.24
			1690		(br s)	(dd, J=9.0, 5.0)	(dd, J=8.0, 5.0)	(m)	(t, J=9.0)
3e	3270	2240	1775	1.32(3H, t, J=7.0)	8.30	1.56-1.90			
			1700	4.27(2H, q, J=7.0)	(br s)		(m)		
3f	3245	2255	1758	3.84(s)	8.40	1.55-1.91			
	3195		1697		(br s)		(m)		

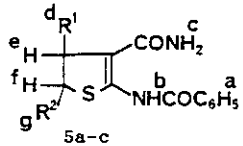
a, b. The assignments may be reversed.

was obtained in 89% yield. On hydrolysis with aq. sodium hydrogen carbonate, **3a** gave 1-cyanocyclopropanecarboxylic acid[5] in 87% yield. On the basis of these data, **2a** was assigned as N-benzoyl-4-chloro-2-cyanobutanamide. Similarly, the reactions of 2-acetamido-4,5-dihydro-3-furancarbonitrile (**1b**), 2-benzamido (or acetamido)-4,5-dihydro-4-phenyl-3-furancarbonitrile (**1c** or **1d**), and ethyl (or methyl) N-2-(3-cyano-4,5-dihydrofuryl)-carbamate (**1e** or **1f**) with titanium (IV) chloride resulted in the formation of the corresponding 4-chloro-2-cyanobutanamides (**2b-f**), which were cyclized by refluxing them with potassium carbonate in acetone to provide the corresponding cyclopropane derivatives (**3b-f**). The structural assignments of these products were made on the basis of the elemental analysis (Table 1) and spectral data (Table 2). Furthermore, the structure of **3c** was confirmed by direct comparison with an authentic sample prepared from N-benzoyl-α-cyanoacetamide[4] and 1,2-dibromo-1-phenylethane. N-Benzoyl (and acetyl)-1-cyano-2-phenylcyclopropanecarboxamides (**3c**, **d**) were hydrolyzed by hot 5% potassium carbonate to give (E)-1-cyano-2-phenylcyclopropanecarboxylic acid.[6] Therefore, both **3c** and **3d** have (E)-configuration.



Scheme 2

Reasonable pathway for the ring opening is shown in Scheme 2. Compound (**1a**) reacted with titanium (IV) chloride to form an oxonium salt (**8**), and then a chloride ion attacked at C-5 of **8** to furnish **9**, which was hydrolyzed to give **2a**. The proposed mechanism is similar to that reported by Olah *et al.*[7] in the case of the reaction of lactones with boron tribromide. On the other hand, the reactions of 2-benzamido-4,5-dihydro-3-thiophene-



5a-c

a : R^1=R^2=H

b : R^1=H, R^2=CH_3

c : R^1=C_6H_5, R^2=H

Table 3. Some Properties of 5a-c

Compd No.	Yield (%)	mp (°C) (Recrystallization solvent)	Appearance (Pale yellow)	Formula	Analysis (%) Calcd (Found) C	H	N
5a	77	222-224 ($CHCl_3$)	Columns	$C_{12}H_{12}N_2O_2S$	58.05 (58.08	4.87 4.82	11.28 11.25)
5b	91	182-183 (acetone)	Columns	$C_{13}H_{14}N_2O_2S$	59.52 (59.35	5.38 5.39	10.68 10.47)
5c	50	221-222 ($CHCl_3$)	Needles	$C_{18}H_{16}N_2O_2S$	66.65 (66.43	4.97 4.83	8.64 8.52)

Table 4. Spectral Data for 5a-c

Compd No.	ir ν_{max}^{KBr} cm^{-1} NH	CO	^1H nmr spectra (ppm) in $CDCl_3$ solution (J in Hz) H^a	H^b	H^c	H^d	H^e	H^f	H^g
5a	3495 3355	1660 1640	7.40-7.65 (3H, m) 7.89-8.07 (2H, m)	13.19 (br s)	5.24 (br s)	2.78-3.01 (m)		3.15-3.38 (m)	
5b	3495 3370	1675 1625	7.35-7.59 (3H, m) 7.86-8.08 (2H, m)	13.17 (br s)	5.43 (br s)	3.07 (dd, J=14.0, 8.5)	2.51 (dd, J=14.0, 6.0)	3.65-3.90 (m)	1.44 (d, J=7.0)
5c	3495 3310	1670 1645	7.35-7.59 (3H, m) 7.97-8.08 (2H, m)	13.50 (br s)	4.99 (br s)	7.35-7.59 (m)	4.33 (dd, J=10.0, 4.5)	3.04 (dd, J=11.5, 4.5)	3.75 (dd, J=11.5, 10.0)

carbonitrile (**4a**) and its 5-methyl or 4-phenyl derivatives (**4b** or **4c**)[8] with titanium (IV) chloride did not give the expected ring opening products, but resulted in the formation of the corresponding 2-benzamido-4,5-dihydro-3-thiophenecarboxamides (**5a-c**). The structures of **5a-c** were confirmed by direct comparison with the authentic samples which were synthesized by the following route: On acidic hydrolysis, 2-amino-4,5-dihydro-3-thiophenecarbonitrile and its 5-methyl or 4-phenyl derivatives[8] were converted to the corresponding tetrahydro-2-oxo-3-thiophenecarbonitriles (**6a-c**). Compounds **6a-c** were allowed to react with ammonium hydroxide according to the method of Campaigne et al.[9] to provide 2-amino-4,5-dihydro-3-thiophenecarboxamides **7a-c**. On treatment with benzoyl chloride in pyridine, **7a-c** gave **5a-c**.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded on an IRA-2 spectrophotometer. ^{1}H Nmr spectra were taken on a Hitachi R-22 spectrometer (90 MHz) with tetramethylsilane as an internal standard. Ms spectra were measured with a JEOL model JMS-D 300 mass spectrometer.

2-Acetamido-4,5-dihydro-3-furancarbonitrile (1b). A suspension of 2-amino-4,5-dihydro-3-furancarbonitrile (1.1 g, 0.1 mol) in Ac_2O (30 ml, 0.32 mol) was heated at 40-50 °C for 2 h, and then cooled. The crystals were collected, washed with ether, and recrystallized from acetone-petr. benzin to yield **1b** (11.2 g, 74%) as colorless prisms, mp 142-143 °C. Anal. Calcd for $C_7H_8N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.53; H, 5.44; N, 18.66. Ms m/z: 152 (M^+). Ir (KBr): 3220, 3140 (NH), 2210 (CN), 1693 cm^{-1} (CO). ^{1}H Nmr ($CDCl_3$) δ: 2.18 (3H, s, CH_3), 2.95 (2H, t, J=9.0 Hz, C_4-H), 4.53 (2H, dd, J=9.5, 9.0 Hz, C_5-H), 8.61 (1H, br s, NH).

2-Acetamido-4,5-dihydro-4-phenyl-3-furancarbonitrile (1d). A suspension of 2-amino-4,5-dihydro-4-phenyl-3-furancarbonitrile (1.86 g, 0.1 mol) in Ac_2O (40 ml, 0.42 mol) was heated at 50-60 °C for 2 h. Work-up as described a-

bove gave **1d**. Recrystallization from acetone-petr. benzin gave **1d** as colorless prisms, 16.92 g (69%), mp 136-138°C. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.51; H, 5.24; N, 12.29. Ms m/z: 228 (M^+). Ir (KBr): 3260, 3160 (NH), 2210 (CN), 1702 cm^{-1}(CO). ^1H Nmr ($CDCl_3$) δ : 2.10 (3H, s, CH_3), 4.24-4.45 (2H, m, C_5-H), 4.72-4.94 (1H, m, C_4-H), 7.14-7.38 (5H, m, aromatic H), 8.73 (1H, br s, NH).

Ethyl (or Methyl) N-2-(3-Cyano-4,5-dihydrofuryl)carbamate (1e or 1f). A solution of ethyl (or methyl) chloroformate (5.97 g or 5.20 g, 55 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a suspension of 2-amino-4,5-dihydro-3-furancarbonitrile (1.1 g, 50 mmol) and pyridine (4.35 g, 55 mmol) in CH_2Cl_2 (50 ml) with stirring and ice-cooling. The mixture was stirred at room temperature for 2 h, poured into ice water, and then extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with CH_2Cl_2 as the eluent.

i) Compound **1e** : Colorless columns (5.16 g, 57%), mp 67-69°C (ether-petr. ether). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.74; H, 5.58; N, 15.38. Ms m/z: 182 (M^+). Ir (KBr): 3320 (NH), 2220 (CN), 1725 cm^{-1}(CO). ^1H Nmr ($CDCl_3$) δ : 1.32 (3H, t, J=7.0 Hz, CH_3), 2.97 (2H, t, J=8.5 Hz, C_4-H), 4.27 (2H, q, J=7.0 Hz, $CO_2\underline{CH_2}CH_3$), 4.53 (2H, t, J=8.5 Hz, C_5-H), 7.24 (1H, br s, NH).

ii) Compound **1f**: Colorless columns (4.28 g, 51%), mp 87-88°C (CH_2Cl_2-petr. benzin). Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.97; H, 4.74; N, 16.66. Ms m/z: 168 (M^+). Ir (KBr): 3290 (NH), 2200 (CN), 1735 cm^{-1} (CO). ^1H Nmr($CDCl_3$) δ : 2.97 (2H, t, J=9.0 Hz, C_4-H), 3.82 (3H, s, CH_3), 4.54 (2H, t, J=9.0 Hz, C_5-H).

Reaction of 1a-f with Titanium (IV) Chloride. General Procedure. Titanium (IV) chloride (2.28 g, 12 mmol) was added dropwise to an ice-cooled and stirred solution of **1a-f** (10 mmol) in $CHCl_3$ (20 ml). After the mixture was refluxed for 1 h, the precipitate was dissolved in 5% HCl (10 ml) with

stirring and ice-cooling, and the $CHCl_3$ layer was separated. The aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ layer and the $CHCl_3$ extract were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to yield **2a-f**. The analytical and spectral data for **2a-f** are given in Tables 1 and 2.

Reaction of N-Benzoyl (or Acetyl)-1-cyanocyclopropanecarboxamide (3a or 3b) with Titanium (IV) Chloride. A solution of **3a** or **3b** (10 mmol) and titanium (IV) chloride (2.28 g, 12 mmol) in $CHCl_3$ (20 ml) was refluxed for 1 h. After the same work-up as noted in the reaction of **1a-f** with titanium (IV) chloride, **2a** or **2b** was obtained in 89% or 82% yield, respectively.

Conversion of 2a-f into 1-Cyanocyclopropanecarboxamides (3a-f). General Procedure. A suspension of **2a-f** (10 mmol) and K_2CO_3 (1.38 g, 10 mmol) in acetone (30 ml) was refluxed for 1 h. After removal of the acetone *in vacuo*, the residue was poured into ice water, acidified with 10% HCl, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized from the solvent indicated in Table 1. The analytical and spectral data for **3a-f** are given in Tables 1 and 2.

Hydrolysis of N-Benzoyl-1-cyanocyclopropanecarboxamide (3a). A suspension of **3a** (2.14 g, 10 mmol) in saturated aq. $NaHCO_3$ (20 ml) was heated at 70-80 °C for 3 h with stirring. The reaction mixture was cooled, and washed with $CHCl_3$ to remove benzamide. The aqueous layer was acidified with 10% HCl, salted out with NaCl, and then extracted with AcOEt. The AcOEt layer was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2 to provide 1-cyanocyclopropanecarboxylic acid (965 mg, 87%) as colorless columns (mp 145-147 °C, lit.[5] mp 142-144 °C). This compound was shown to be identical with an authentic sample[5] by mixed melting point determination and comparison of the ir spectra.

Hydrolysis of 3c or 3d. A suspension of **3c** or **3d** (5 mmol) in 5% K_2CO_3 (10 ml) was heated at 80 °C for 2 h. Work-up as described above gave (E)-1-cyano-2-phenylcyclopropanecarboxylic acid (mp 136-137 °C, lit.[6] 137-138 °C) in 65% or 67% yield, respectively. This compound was shown to be identical with an authentic sample[6] by mixed melting point determination and comparison of the ir spectra.

Preparation of N-Benzoyl-1-cyanocyclopropanecarboxamide (3a). 60% Sodium hydride (0.4 g, 10 mmol) was added to a solution of N-benzoyl-α-cyanoacetamide (1.18 g, 10 mmol) in DMF (20 ml) with stirring and ice-cooling. The stirring was continued at room temperature until evolution of gas ceased, and a solution of 1,2-dibromoethane (2.07 g, 11 mmol) in DMF (5 ml) was added. The whole was stirred at room temperature for another 30 min and 60% sodium hydride (0.8 g, 20 mmol) was added under ice-cooling, and the reaction mixture was stirred at room temperature for 1 h. After removal of the solvent in vacuo, ice water was added to the residue and the mixture was acidified with 10% HCl. The deposited crystals were collected, washed with water, dried, and subjected to silica gel column chromatography. Elution with $CHCl_3$ gave **3a** (1.19 g, 56%), which was recrystallized from acetone-petr. benzin to provide colorless needles, mp 125-126 °C.

Preparation of (E)-N-Benzoyl-1-cyano-2-phenylcyclopropanecarboxamide (3c). 60% Sodium hydride (0.4 g, 10 mmol) was added to an ice-cooled solution of N-benzoyl-α-cyanoacetamide (1.88 g, 10 mmol) in DMF (5 ml), and a solution of 1,2-dibromo-1-phenylethane (2.9 g, 11 mmol) in DMF (5 ml) was added. The reaction mixture was heated at 40-50 °C for 1 h and then 60% sodium hydride (0.8 g, 20 mmol) was added under ice-cooling. The whole was heated at 40-50 °C for another 1 h. Work-up as described above gave **3c** (0.29 g, mp 135-136 °C) in 10% yield.

Reaction of 4a-c with Titanium (IV) Chloride. Titanium (IV) chloride (3.8 g, 20 mmol) was added dropwise to an ice-cooled solution of **4a**, **4b** or **4c**

(10 mmol) in 1,2-dichloroethane (20 ml). The mixture was refluxed for 2 h (in the case of **4a** and **4b**) or 10 h (in the case of **4c**). After the same work-up as noted in the reaction of **1a-f** with titanium (IV) chloride, **5a-c** were obtained. These compounds were identical with the authentic samples prepared by the method described later. The analytical and spectral data for **5a-c** are given in Tables 3 and 4.

Tetrahydro-2-oxo-3-thiophenecarbonitriles (6a-c). A suspension of 2-amino-4,5-dihydro-3-thiophenecarbonitrile or 2-amino-4,5-dihydro-5-methyl-3-thiophenecarbonitrile (10 mmol) in 5% HCl (10 ml) was heated at 60 °C for 30 min. The reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4, and concentrated in vacuo.

i) The residue was recrystallized from CH_2Cl_2-petr. ether to give tetrahydro-2-oxo-3-thiophenecarbonitrile (**6a**) as colorless columns, 1.17 g (92%), mp 51-52 °C. Anal. Calcd for C_5H_5NOS: C, 47.23; H, 3.96; N, 11.01. Found: C, 47.31; H, 3.98; N, 11.07. Ms m/z: 127 (M^+). Ir (KBr): 2230 (CN), 1750 cm^{-1}(CO). ^1H Nmr ($CDCl_3$) δ: 2.26-2.96 (2H, m, C_4-H), 3.26-3.75 (3H, m, C_3-H and C_5-H).

ii) The residue was purified by column chromatography on silica gel with ether as the eluent to give tetrahydro-5-methyl-2-oxo-3-thiophenecarbonitrile (**6b**) as colorless oil, bp 140-150 °C (oil bath temperature), 1.27 g (90%). Anal. Calcd for C_6H_7NOS : C, 51.04; H, 5.00; N, 9.92. Found: C, 50.85; H, 4.97; N, 10.19. Ms m/z : 141 (M^+). Ir (neat): 2230 (CN), 1700 cm^{-1}(CO). ^1H Nmr ($CDCl_3$) δ : 1.55 (3H, d, J=6.6 Hz, CH_3), 1.90-3.00 (2H, m, C_4-H), 3.75 (1H, dd, J=14.0, 6.6 Hz, C_3-H), 3.70-4.30 (1H, m, C_5-H).

iii) A suspension of 2-amino-4,5-dihydro-4-phenyl-3-thiophenecarbonitrile (2.02 g, 10 mmol) in $CHCl_3$ (5 ml) and 10% HCl (10 ml) was refluxed for 1 h. After work-up as noted in i), tetrahydro-2-oxo-4-phenyl-3-thiophenecarbonitrile (**6c**) was obtained. Recrystallization from acetone-petr. benzin gave **6c** (1.84 g, 91%) as colorless columns, mp 108-109 °C. Anal. Calcd for $C_{11}H_9NOS$: C, 64.77; H, 4.32; N, 6.79. Found: C, 65.00; H, 4.46; N, 6.89.

Ms m/z: 203 (M^+). Ir (KBr): 2230 (CN), 1700 cm^{-1}(CO). ^1H Nmr ($CDCl_3$) δ: 3.50-4.00 (4H, m, C_3-H, C_4-H, and C_5-H), 7.30-7.55 (5H, aromatic H).

2-Amino-4,5-dihydro-3-thiophenecarboxamides (7a-c). A suspension of **6a**, **6b** or **6c** (20 mmol) in conc. NH_4OH (10 ml) was stirred at room temperature for 1 h. The reaction mixture was cooled, and the precipitate was collected, washed with water, and then dried.

i) 2-Amino-4,5-dihydro-3-thiophenecarboxamide (**7a**): Colorless scales (2.32 g, 81%), mp 138-139 °C (acetone). Anal. Calcd for $C_5H_8N_2OS$: C, 41.65; H, 5.59; N, 19.43. Found: C, 41.65; H, 5.67; N, 19.31. Ms m/z: 144 (M^+). Ir (KBr) : 3400, 3270, 3180 (NH), 1640 cm^{-1}(CO). ^1H Nmr [$(CD_3)_2SO$] δ: 2.68-2.88 (2H, m, C_4-H), 2.99-3.17 (2H, m, C_5-H), 6.17 (2H, br s, NH_2), 7.26 (2H, br s, NH_2).

ii) 2-Amino-4,5-dihydro-5-methyl-3-thiophenecarboxamide (**7b**): Colorless prisms (1.62 g, 51%), mp 135-136 °C (acetone-petr. benzin). Anal. Calcd for $C_6H_{10}N_2OS$: C, 45.55; H, 6.37; N, 17.71. Found : C, 45.63; H, 6.56; N, 17.47. Ms m/z: 158 (M^+). Ir (KBr): 3470, 3360, 3250, 3160 (NH), 1610 cm^{-1} (CO). ^1H Nmr ($CDCl_3$) δ: 1.43 (3H, d, J=7.0 Hz, CH_3), 2.54 (1H, dd, J=12.0, 6.0 Hz, C_4-H), 3.07 (1H, dd, J=12.5, 7.5 Hz, C_4-H), 3.56-3.90 (1H, m, C_5-H), 5.07 (2H, br s, NH_2), 6.37 (2H, br s, NH_2).

iii) 2-Amino-4,5-dihydro-4-phenyl-3-thiophenecarboxamide (**7c**): Colorless columns (3.89 g, 88%), mp 171-172 °C (acetone). Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.98; H, 5.49; N, 12.72. Found: C, 60.08; H, 5.53; N, 12.77. Ms m/z: 220 (M^+). Ir (KBr): 3465, 3380, 3260, 3160 (NH), 1635 cm^{-1}(CO). ^1H Nmr ($CDCl_3$) δ : 2.95 (1H, dd, J=7.0, 4.0 Hz, C_5-H), 3.71 (1H, dd, J=11.0, 9.0 Hz, C_5-H), 4.34 (1H, dd, J=8.5, 4.0 Hz, C_4-H), 4.68 (2H, br s, NH_2), 6.62 (2H, br s, NH_2), 7.32 (5H, s, aromatic H).

2-Benzamido-4,5-dihydro-3-thiophenecarboxamides (5a-c). Benzoyl chloride (1.69 g, 12 mmol) was added to an ice-cooled solution of **7a**, **7b** or **7c** (10 mmol) in pyridine (10 ml). The reaction mixture was stirred at 40-50 °C for 1 h and poured into ice water. The precipitate was collected, washed with

water, dried and recrystallized from the solvent listed in Table 3. Yields were 81% (**5a**), 87% (**5b**), and 87% (**5c**), respectively.

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