Preparation and Hydrolysis of 2-Cyano and 3-Cyano Derivatives of Furo[3,2-*b*]-, Furo[2,3-*c*]- and Furo[3,2-*c*]pyridine

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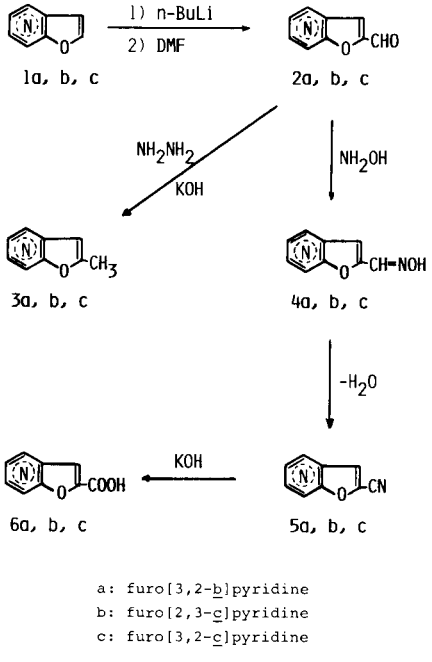
Received July 24, 1986

This paper describes the preparation and hydrolysis of 2-cyano and 3-cyano derivatives of furo[3,2-*b*]-, furo[2,3-*c*]- and furo[3,2-*c*]pyridine. Treatment of furopyridines **1a**, **1b** and **1c** with *n*-butyllithium in hexane-tetrahydrofuran at -70° and subsequent addition of *N*,*N*-dimethylformamide yielded 2-formyl derivatives **2a**, **2b** and **2c**. Dehydration of the oximes **4a**, **4b** and **4c** of **2a**, **2b** and **2c** gave 2-cyano compounds **5a**, **5b** and **5c**, which were hydrolyzed to give 2-carboxylic acids, **6a**, **6b** and **6c**, respectively. Reaction of 3-bromo compounds **7a**, **7b** and **7c** with copper(I) cyanide in *N*,*N*-dimethylformamide afforded 3-cyano derivatives **8a**, **8b** and **8c**. Alkaline hydrolysis of **8a**, **8b** and **8c** gave compounds formed by fission of the 1-2 bond of furopyridines **9a**, **9b** and **9c**, while acidic hydrolysis gave the corresponding carboxamides, **10a**, **10b** and **10c**.

J. Heterocyclic Chem., **24**, 373 (1987).

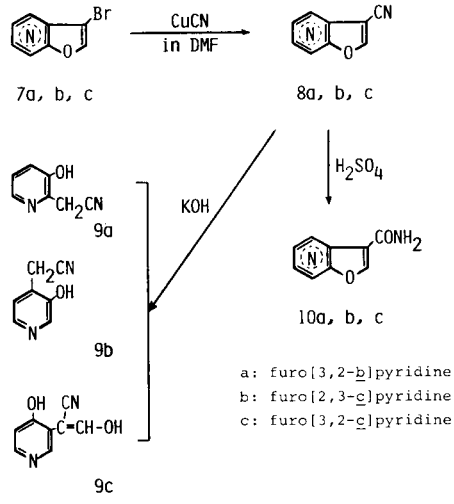
In the previous paper [1] we reported the preparation and hydrolysis of 2-cyano- and 3-cyanofuro[2,3-*b*]pyridine. The 2-cyano derivative was obtained by formylation of furo[2,3-*b*]pyridine *via* 2-lithio intermediate, oximation of the aldehyde and dehydration of the aldoxime, while the 3-cyano compound was prepared by nucleophilic substitution of 3-bromofuro[2,3-*b*]pyridine with copper(I) cyanide in *N*,*N*-dimethylformamide. Alkaline hydrolysis of 3-cyano compound gave a mixture of 1-[3-(2-hydroxypyridyl)]-2-ethoxyacrylonitrile and 3-cyanomethylpyridin-2-ol, while the 2-cyano compound gave the corresponding 2-carboxylic acid.



Scheme 1

Analogously, it is predicted that 2-cyano and 3-cyano derivatives of furo[3,2-*b*]-, furo[2,3-*c*]- and furo[3,2-*c*]pyridine should exhibit closely similar behavior. The present study is an attempt to probe the accuracy of this prediction.

The parent compounds, **1a**, **1b** and **1c**, were treated with *n*-butyllithium in hexane (molar ratio BuLi: **1a**, **1b** or **1c** = 1.16) in tetrahydrofuran at -70° to give the 2-lithio intermediate *in situ*, and subsequently reacted with *N*,*N*-dimethylformamide to afford 2-formyl derivatives, **2a**, **2b** and **2c**, respectively, in 75.6%, 81% and 92% yield. Under these conditions, no addition of BuLi to the heterocyclic nitrogen is noted, which was discussed by Klemm for thieno[2,3-*b*]pyridine [2] and Gronowitz and Sandberg for thieno[2,3-*c*]- and thieno[3,2-*c*]pyridine [3]. The aldehydes were easily reduced to 2-methyl derivatives, **3a**, **3b** and **3c**, by Wolff-Kishner reduction. The aldoximes, **4a**, **4b** and **4c**, were prepared from **2a**, **2b** and **2c**, respectively, by the conventional procedure. Dehydration of **4b** and



Scheme 2

Table I

Physical Data of Some 2- and 3-Substituted Derivatives of Furo[3,2-*b*]-, Furo[2,3-*c*]- and Furo[3,2-*c*]pyridine

Compound No.	Mp. °C	Solvent	Yield (%)	Molecular Formula	Analysis % (Calcd./Found) C	H	N	IR (cm^{-1})	Mass spectrum (m/e)
2a	141.5-142	DME-hexane	75.6	$C_8H_5NO_2$	65.31	3.43	9.52	1680 (CHO)	147 (M^+), 146, 119,
					65.60	3.49	9.75		91, 90, 65, 64
2b	120.5-121	Ether	81	$C_8H_5NO_2$	65.31	3.43	9.52	1675 (CHO)	147 (M^+), 146, 119,
					65.17	3.56	9.33		118, 91, 64
2c	129.5-130	Ether	92	$C_8H_5NO_2$	65.31	3.43	9.52	1665 (CHO)	147 (M^+), 146, 119,
					65.32	3.66	9.54		91, 90, 64, 63
4a	195-196	Methanol	91	$C_8H_6N_2O_2$	59.20	3.73	17.28		162 (M^+), 144, 119,
					59.34	3.82	17.09		91,90
4b	210-211	Methanol	98	$C_8H_6N_2O_2$	59.20	3.73	17.28		162 (M^+), 144, 119,
					59.34	3.91	17.15		91, 90
4c	204-205	Methanol	95	$C_8H_6N_2O_2$	59.20	3.73	17.28		162 (M^+), 144, 119,
					59.01	3.91	17.02		91, 90, 89
5a	68.5-70.5	Ether	64	$C_8H_4N_2O$	66.67	2.80	19.44	2230 (CN)	144 (M^+), 116, 89
					66.90	3.00	19.24		
5b	128-130	Ether	73	$C_8H_4N_2O$	66.67	2.80	19.44	2240 (CN)	144 (M^+), 117, 116,
					66.85	2.84	19.20		89,88
5c	63.5-66	Ether	65	$C_8H_4N_2O$	66.67	2.80	19.44	2240 (CN)	144 (M^+), 117, 116,
					66.51	3.02	19.22		89
6a	>320	Water	95	$C_8H_5NO_3$	58.90	3.09	8.59	2550-2350	
					58.63	3.01	8.64	1720 (−COOH)	
6b	>320	Water	95	$C_8H_5NO_3$	58.90	3.09	8.53	1640 (COO^-)	
					58.93	3.18	8.32		
6c	>320	Ethanol Water	91	$C_8H_5NO_3 \cdot \frac{1}{4}H_2O$	57.32	3.31	8.30	1700 (COOH)	
					57.28	3.05	8.53		
8a	146-147	Ether	51	$C_8H_4N_2O$	66.67	2.80	19.44	2230 (CN)	144 (M^+), 116, 89,
					66.50	2.98	19.55		88, 64, 63, 62
8b	121-122	Ether	55	$C_8H_4N_2O$	66.67	2.80	19.44	2250 (CN)	144 (M^+), 117, 116,
					66.81	2.77	19.31		89, 88, 63, 62
8c	129-130	Ether	80	$C_8H_4N_2O$	66.67	2.80	19.44	2240 (CN)	144 (M^+), 117, 116
					66.50	2.83	19.15		89, 88, 63, 62
9a	143-145	Acetone	66	$C_7H_6N_2O$	62.68	4.51	20.88	2250 (CN)	134 (M^+), 107, 79,
					62.57	4.59	20.55	3300-2200	52
9b	175-178	Acetone	68	$C_7H_6N_2O$	62.68	4.51	20.88	2250 (CN)	134 (M^+), 107, 79,
					62.70	4.65	20.66	2800-2200	52
9c	225-227	Methanol	85	$C_8H_6N_2O_2$	59.20	3.73	17.28	2210 (CN)	162 (M^+), 161, 144,
					58.85	3.81	17.14	3400-2400	134, 133, 117, 106
10a	160-161	Methanol	89	$C_8H_6N_2O_2$	59.20	3.73	17.28	1675 ($CONH_2$)	
					59.49	3.83	17.24		
10b	227-229	Acetone	92	$C_8H_6N_2O_2$	59.20	3.73	17.28	1665 ($CONH_2$)	
					59.14	3.76	17.04		
10c	241-242	Methanol	90	$C_8H_6N_2O_2$	59.20	3.73	17.28	1670 ($CONH_2$)	
					59.22	3.86	17.26		

4c by refluxing with acetic anhydride in the presence of *p*-toluensulfonic acid yielded the corresponding 2-cyano compound **5b** and **5c**, while the dehydration of **4a** to obtain **5a** was performed by refluxing with 2,4,6-trichloro-*s*-trizaine in dichloromethane [4].

Nucleophilic substitution of 3-bromo compounds, **7a**, **7b** and **7c** [5] with copper(I) cyanide in refluxing *N*,*N*-dimethylformamide gave the corresponding 3-cyano derivatives, **8a**, **8b** and **8c**.

The alkaline hydrolysis of 2-cyano compounds afforded 2-carboxylic acids, **6a**, **6b** and **6c**, in high yield respectively. Whereas, the hydrolysis of 3-cyano compounds with potassium hydroxide in aqueous ethanol afforded compounds formed by fission of the 1-2 bond of the furopyridines: 2-cyanomethylpyridine-3-ol (**9a**) from **8a**, 4-cyanomethylpyridin-3-ol (**9b**) from **8b** abd 1-[3-(4-hydroxypyridyl)]-2-hydroxyacrylonitrile (**9c**) from **8c** in moderate yield. The structure of **9a**, **9b** and **9c** were confirmed from their elemental analyses and ir, ^1H nmr and mass spectra. Compound **9a**, $C_7H_6N_2O$ (MW: 134), showed absorption due to ν OH at 3300-2200 cm^{-1} (broad) and ν CN at 2250 cm^{-1} in its ir spectrum, and exhibited signals of protons attached to the pyridine ring at δ 7.12 (dd, J = 3.4, 5.4 Hz, 1H, H-5), 7.16 (dd, J = 2.5, 5.4 Hz, 1H, H-4) and 8.01 (dd, J = 2.8, 3.4 Hz, 1H, H-6) and of methylene protons at δ 3.86 (s, 2H, this signal disappeared in deuteriometh

Table II

^{1}H NMR Data of Some 2- and 3-Substituted Derivatives of Furo[3,2-*b*]-, Furo[2,3-*c*]- and Furo[3,2-*c*]pyridine

Compound No.	H-2	H-3	H-4	H-5	H-6	H-7	Others
2a [a]	–	7.68 (d) J = 0.8	–	8.67 (dd) J = 4.6, 1.8	7.37 (dd) J = 8.6, 4.6	7.87 (dq) J = 8.6, 1.8, 0.8	9.89 (s) (-C*H*O)
2b [a]	–	7.53 (s) J = 5.4	7.67 (d) J = 5.4	8.53 (d)	–	9.04 (s)	9.96 (s) (-C*H*O)
2c [a]	–	7.62 (d) J = 0.8	9.09 (d) J = 0.8	–	8.64 (d) J = 5.8	7.53 (dt) J = 5.8, 0.8	9.88 (s) (-C*H*O)
4a [b]	–	7.10 (d) J = 0.8	–	8.49 (dd) J = 4.6, 1.2	7.30 (dd) J = 8.0, 4.6	7.88 (dq) J = 8.0, 1.2, 0.8	8.10 (s) (-C*H*=NOH)
4b [b]	–	7.06 (d) J = 0.8	7.64 (dd) J = 5.2, 0.8	8.29 (d) J = 5.2	–	8.76 (t) J = 0.8	8.13 (s) (-C*H*=NOH)
4c [b]	–	7.11 (s)	8.83 (s)	–	8.37 (d) J = 6.0	7.53 (d) J = 6.0	8.09 (s) (-C*H*=NOH)
5a [a]	–	7.60 (d) J = 0.8	–	8.68 (dd) J = 4.4, 1.2	7.38 (dd) J = 8.4, 4.4	7.82 (dq) J = 8.4, 1.2, 0.8	–
5b [a]	–	7.40 (d) J = 0.8	7.56 (dd) J = 5.0, 0.8	8.49 (d) J = 5.0	–	8.93 (t) J = 0.8	–
5c [a]	–	7.51 (d) J = 0.8	9.02 (d) J = 0.8	–	8.65 (d) J = 5.6	7.48 (dt) J = 5.6, 0.8	–
6a [c]	–	7.70 (d) J = 0.8	–	8.60 (dd) J = 4.6, 1.4	7.45 (dd) J = 8.6, 4.6	8.12 (dq) J = 8.6, 1.4 0.8	–
6b [c]	–	7.70 (d) J = 0.8	7.82 (dd) J = 5.4, 0.8	8.50 (d) J = 5.4	–	9.09 (t) J = 0.8	–
6c [c]	–	7.76 (d) J = 0.8	9.10 (s)	–	8.60 (d) J = 5.0	7.77 (dd) J = 5.0, 0.8	–
8a [a]	8.26 (s)	–	–	8.63 (dd) J = 4.8, 1.2	7.32 (dd) J = 8.4, 4.8	7.78 (dd) J = 8.4, 1.2	–
8b [a]	8.30 (s)	–	7.68 (d) J = 5.2	8.57 (d) J = 5.2	–	8.98 (s)	–
8c [a]	8.16 (s)	–	9.10 (d) J = 0.8	–	8.66 (d) J = 6.0	7.54 (dd) J = 6.0, 0.8	–
9a [d]	–	–	7.16 (dd) J = 5.4, 2.8	7.12 (dd) J = 5.4,3.4	8.01 (dd) J = 3.4,2.8	–	3.86 (s, 2H) (-CH_2CN)
9b [d]	8.12 (s)	–	–	7.21 (d) J = 5.0	8.04 (d) J = 5.0	–	3.70 (s, 2H) (-CH_2CN)
9c [c]	7.81 (d) J = 1.4	–	–	6.53 (d) J = 8.4	7.90 (dd) J = 8.4, 1.4	–	7.47 (s, 1H) (-C=C*H*OH)
10a [a]	8.44 (s)	–	–	8.51 (dd) J = 4.8, 1.4	7.24 (dd) J = 8.2, 4.8	7.78 (dd) J = 8.2, 1.4	6.37 (2H, broad s) (-CONH_2)
10b [b]	8.50 (s)	–	8.05 (d) J = 5.4	8.40 (d) J = 5.4	–	8.83 (s)	–
10c [b]	8.35 (s)	–	9.20 (d) J = 0.8	–	8.42 (d) J = 6.0	7.56 (dd) J = 6.0, 0.8	–

[a] in deuteriochloroform; [b] in deuteriomethanol; [c] in dimethylsulfoxide-d_6; [d] in deuterioacetonitrile.

anol by the exchange with deuterium of the solvent) in the ^{1}H nmr spectrum (in deuterioacetonitrile). Compound **9b**, $C_7H_6N_2O$ (MW: 134), showed ν OH at 2800-2200 (broad), 2000-1600 cm^{-1} (broad) and ν CN at 2250 cm^{-1} in the ir spectrum, and showed signals of pyridine ring protons at δ 7.21 (d, J = 5.0 Hz, 1H, H-5), 8.04 (d, J = 5.0 Hz, 1H, H-6) and 8.12 (s, 1H, H-2) and of methylene protons at δ 3.70 (s, 2H, this signal disappeared in deuteriomethanol) in the ^{1}H nmr spectrum (in deuterioacetonitrile). The ir spectrum of compound **9c**, $C_8H_6N_2O_2$ (MW: 162), showed ν OH at 3400-2400 cm^{-1} (broad) and ν CN at 2210 cm^{-1}. In the ^{1}H nmr spectrum the signals of protons attached to the pyridine ring appeared at δ 6.53 (d, J = 8.4 Hz, 1H, H-4), 7.81 (d, J = 1.4 Hz, 1H, H-2) and 7.90 (dd, J = 1.4, 8.4 Hz, 1H, H-6) and that of methine proton at δ 7.47 (s, 1H).

These results are much similar to that of 3-cyanofuro-[2,3-*b*]pyridine [1]. Thus, it is apparent that 2-position of 3-cyanofuropyridines is highly reactive to nucleophilic at-

tack and the bond at 1-2 is easily cleaved.

Contrarily, hydrolysis of these 3-cyano compounds with sulfuric acid afforded 3-carboxamides **10a**, **10b** and **10c** in fairly good yield.

EXPERIMENTAL

The melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. The ir spectra were obtained with a JASCO A-102 spectrometer. The ^{1}H nmr spectra were recorded on a JEOL JNM-PMX-60 instrument using tetramethylsilane as an internal standard. Mass spectra were obtained with a ESCO EMD-05B instrument.

2-Formylfuro[3,2-*b*]- (**2a**), 2-Formylfuro[2,3-*c*]- (**2b**) and 2-Formylfuro-[3,2-*c*]pyridine (**2c**).

General Procedure.

A solution of furopyridine (**1**) (3.0 g, 25 mmoles) in 60 ml of dry tetrahydrofuran was stirred under nitrogen atmosphere and maintained at -70° while a solution of *n*-butyllithium in hexane (18 ml, 1.6*M*, 29 mmoles) was added dropwise by syringe over a period of 10 minutes. After stirring at this temperature for 5 minutes, the colored (dark-green for **1a**, wine-red for **1b** and light-green for **1c**) mixture was treated with *N*,*N*-dimethylformamide (3.6 g, 49 mmoles). The reaction mixture was stirred for 10 hours after removal of the cooling bath. Then, the mixture was treated with 10% hydrochloric acid, made alkaline with sodium bicarbonate and extracted with dichloromethane. After evaporation of the solvent *in vacuo*, the residue was recrystallized from 1,2-dimethoxyethane-hexane or ether to give 2-formyl compounds. Compounds thus obtained are listed in Table I.

General Procedure for Wolff-Kishner Reduction of 2-Formyl Derivatives **2a**, **2b** and **2c**.

A mixture of **2** (0.5 g, 3.4 mmoles), hydrazine hydrate (1.7 g, 34 mmoles) and potassium hydroxide (1.0 g, 18 mmoles) in 20 ml of ethanol was refluxed on a water bath for 1 hour. After cooling, the mixture was diluted with 50 ml of water and extracted with dichloromethane. The extract was dried (potassium carbonate), and evaporated the solvent. The residual oil was distilled under reduced pressure to give 2-methyl derivatives, **3a**, **3b** and **3c**. Compound **3a** had bp 120-125° (22 mmHg), 93% yield. Compound **3b** had bp 130-133° (35 mm Hg), 95% yield. Compound **3c** had bp 110° (20 mmHg), 92% yield. The ir and ^{1}H nmr spectra were identical with those of the samples prepared by the methods previously reported ([6] for **3a**, [7] for **3b** and [8] for **3c**, respectively).

General Procedure for the Preparation of the Oximes **4a**, **4b** and **4c** of 2-Formylfuropyridines.

To a warm solution of **2** (1.0 g, 6.8 mmoles) in 15 ml of ethanol was added a solution of hydroxylamine hydrochloride (1.0 g, 14.4 mmoles) in 2 ml of water and a solution of potassium carbonate (1.0 g, 7.2 mmoles) in 5 ml of water. After standing at room temperature for 2 hours, the reaction mixture was diluted with 20 ml of water to precipitate the oxime. The oximes prepared by this procedure are listed in Table I.

2-Cyanofuro[3,2-*b*]pyridine (**5a**).

A mixture of **4a** (260 mg, 1.6 mmoles), 2,4,6-trichloro-*s*-triazine (250 mg, 1.36 mmoles), pyridine (0.25 ml) in 20 ml of dichloromethane was stirred and refluxed under nitrogen atmosphere for 1.5 hours. After cooling, to the mixture was added 6 ml of 1*N* sodium hydroxide solution and the mixture was stirred at room temperature for 10 minutes, separated the layers, and extracted the aqueous layer with chloroform. The combined organic layer and extract were dreid (magnesium sulfate) and evaporated the solvent to give crude **5a** which was recrystallized from ether to give 150 mg (64%) of pure **5a**.

2-Cyanofuro[2,3-*c*]- (**5b**) and 2-Cyanofuro[3,2-*c*]pyridine (**5c**).

A solution of **4b** or **4c** (200 mg, 1.23 mmoles) and *p*-toluenesulfonic acid (200 mg) in 10 ml of acetic anhydride was refluxed with stirring for 5 hours. After evaporation of the acetic anhydride *in vacuo*, the dark-brown residue was treated with 30 ml of water, basified with sodium bicarbonate and extracted with chloroform. Drying (magnesium sulfate) and evaporation of the solvent yielded crude **5b** or **5c**. Recrystallization of the crude product from ether gave a pure sample. Compound **5a**, **5b** and **5c** are listed in Table I.

Furo[3,2-*b*]pyridine-2-carboxylic Acid (**6a**), Furo[2,3-*c*]pyridine-2- carboxylic Acid (**5b**) and Furo[3,2-*c*]pyridine-2-carboxylic Acid (**5c**).

General Procedure.

A solution of 2-cyano compound **5** (100 mg, 0.7 mmole) and potassium hydroxide (100 mg, 1.8 mmoles) in aqueous ethanol 70%, 10 ml) was refluxed for 2 hours. After evaporation of the solvent *in vacuo*, the residual solid mass was dissolved in 2 ml of water acidified with hydrochloric acid (*p*H 2-3) and stood overnight in a refrigerator to complete the precipitation. The crystalline precipitates were filtered and recrystallized from water. The carboxylic acids obtained by this procedure are listed in Table I.

3-Cyanofuro[3,2-*b*]- (**8a**), 3-Cyanofuro[2,3-*c*]- (**8b**) and 3-Cyanofuro[3,2-*c*]-pyridine (**8c**).

General Procedure.

A mixture of 3-bromo compound **7** (1.0 g, 5.1 mmoles) and copper(I) cyanide (1.0 g, 11.2 mmoles for **7a** and **7c**, 5.0 g, 56 mmoles for **7b**) in *N*,*N*-dimethylformamide (5 ml) was refluxed with stirring for several hours (2 hours for **7a**, 3 hours for **7b** and 5 hours for **7c**). After cooling, the reaction mixture was diluted with 15% potassium cyanide solution (50 ml), extracted with chloroform and dried (magnesium sulfate). The residue of the chloroform extract was redissolved in ether, washed with water, dried over magnesium sulfate and evaporated the solvent. Recrystallization from ether gave pure samples of 3-cyano compounds **8a**, **8b** and **8c** which are listed in Table I.

Alkaline Hydrolysis of 3-Cyano Derivatives, **8a**, **8b** and **8c**.

General Procedure.

To a solution of 3-cyano compound **8** (100 mg, 0.7 mmole) in 10 ml of ethanol was added a solution of potassium hydroxide (100 mg, 1.8 mmoles) in 4 ml of water, and the mixture was refluxed for 1 hour. After evaporation of the solvent, the solid residue was dissolved in 1 ml of water, acidified with 1*N* hydrochloric acid to *p*H 3-4 and evaporated to dryness. The solid mass was extracted with hot acetone (5 x 10 ml). The residue of the acetone extracts was recrystallized from acetone or methanol to give a pure sample of compound **9a**, **9b** or **9c**, which are listed in Table I.

Acidic Hydrolysis of Compound **8a**, **8b** and **8c**.

General Procedure.

A mixture of compound **8** (100 mg, 0.7 mmole), water (0.2 ml) and sulfuric acid (1 ml) was heated on a water bath for 2 hours. The mixture was cooled, diluted with water, basified with sodium bicarbonate, extracted with chloroform, and dried (magnesium sulfate). After evaporation of the solvent, the residual solid was recrystallized from methanol or acetone. The 3-carboxamides prepared by this procedure are listed in Table I.

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