

**RING CONVERSION OF 2-AMINO-4,5-DIHYDRO-3-FURANCARBONITRILES  
CATALYZED BY HALIDE IONS**

Kenji Yamagata, Hiroshi Maruoka, Yoshichika Hashimoto,  
and Motoyoshi Yamazaki\*

Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1  
Nanakuma, Jonan-ku, Fukuoka 814-01, Japan

**Abstract** — The reaction of 2-amino-4,5-dihydro-3-furancarbonitrile (**1a**) with methylamine hydrochloride in dimethylformamide gave 1-cyano-N-methylcyclopropanecarboxamide (**2**). Similarly, 2-amino-4,5-dihydro-4-phenyl( and 5-phenyl)-3-furancarbonitriles [(**1b**) and (**1c**)] provided (E)-1-cyano-N-methyl-2-phenylcyclopropanecarboxamide (**3**). Compound **1b** reacted with sodium iodide to give (E)-1-cyano-2-phenylcyclopropanecarboxamide (**6**). On the other hand, 2-benzamido-4,5-dihydro-3-furancarbonitrile (**7a**) reacted with sodium iodide to furnish 1-benzoyl-2-oxo-3-pyrrolidinedicarbonitrile (**8**).

Helmerts<sup>1)</sup> has reported that 1-amino-2-cyano-1-cyclopentene reacts with dimethylamine hydrochloride to give 2-cyano-1-dimethylamino-1-cyclopentene. In order to prepare 4,5-dihydro-2-methylamino-3-furancarbonitrile, we investigated the reaction of 2-amino-4,5-dihydro-3-furancarbonitrile (**1a**)<sup>2)</sup> with methylamine hydrochloride, and found another novel reaction.

The reaction of **1a** with methylamine hydrochloride (2 eq.) in dimethylformamide (DMF) at 120°C for 2 h did not give the desired 4,5-dihydro-2-methylamino-3-furancarbonitrile (**4a**) but afforded 1-cyano-N-methylcyclopropanecarboxamide (**2**) in 50% yield (Chart 1).

Similarly, both 2-amino-4,5-dihydro-4-phenyl( and 5-phenyl)-3-furancarbonitriles [(**1b**) and (**1c**)]<sup>2)</sup> were allowed to react with methylamine hydrochloride to give the same compound, (E)-1-cyano-N-methyl-2-phenylcyclopropanecarboxamide (**3**) in 33% and 41% yields, respectively.

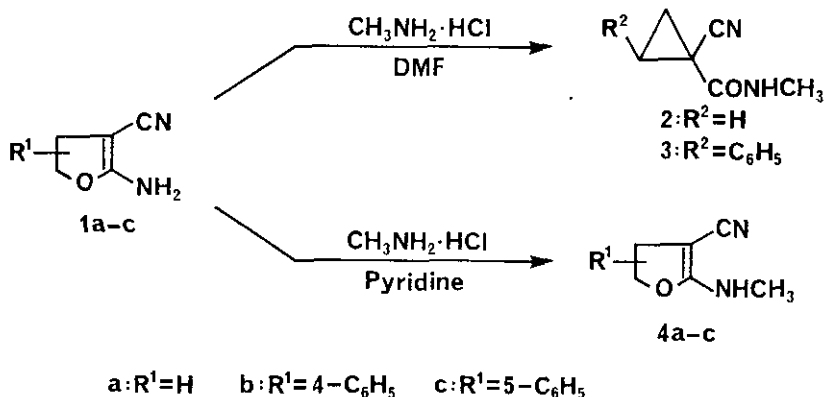


Chart 1

The structures of **2** and **3** were confirmed by direct comparison with those of authentic samples, which were prepared by the following route; On chlorination with thionyl chloride, 1-cyanocyclopropanecarboxylic acid<sup>3)</sup> and (E)-1-cyano-2-phenylcyclopropanecarboxylic acid<sup>4)</sup> were converted to the corresponding acid chlorides, which reacted with methylamine to give **2** and **3**. Reasonable pathway for this ring contraction is shown in Chart 2.

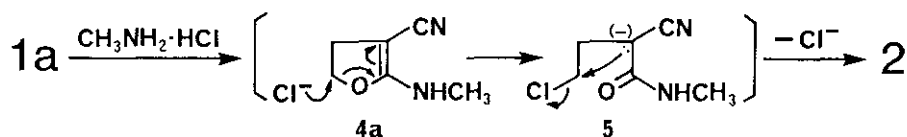


Chart 2

The reaction of **1a** with methylamine hydrochloride gives initially 4,5-dihydro-2-methylamino-3-furancarbonitrile (**4a**), and then chloride ion attacks position 5 of **4a** to give the carbanion (**5**), which undergoes intramolecular cyclization to form **2**.

In order to get an evidence for the proposed mechanism, we examined the reaction of **1b** with other halides. A solution of **1b** and sodium iodide, sodium bromide or sodium chloride in DMF was heated at 120°C for 9 h, yielding (E)-1-cyano-2-phenylcyclopropanecarboxamide (**6**) (mp 184-185°C, lit.<sup>4)</sup> mp 184-185°C). The results are summarized in Table. Sodium iodide was the most effective for the formation of **6**.

Table Reaction of **1b** with NaX


Exp. No.	NaX	Molar ratio NaX / <b>1b</b>	Solvent	Reaction conditions		Yield of <b>6</b> (%)
				Temp(°C)	Time(h)	
1	NaI	2	DMF	120	9	62
2	NaBr	2	DMF	120	9	43
3	NaCl	2	DMF	120	9	7 <sup>*)</sup>
4	NaI	1.1	DMSO	160	5	46
5	NaBr	1.1	DMSO	160	5	46
6	NaBr	1.1	DMF	reflux	4	48
7	NaBr	1.1	DMF	120	5	49

\*) The starting material was recovered in 40% yield

On the other hand, the reaction of **1b** with methylamine hydrochloride in pyridine instead of DMF proceeded to furnish 4,5-dihydro-2-methylamino-4-phenyl-3-furancarboxitrile (**4b**) in 64% yield, and no formation of **3** was apparent. Compound **4b** reacted with sodium iodide to give **3** in 64% yield.

Subsequently, with the aim of widening the scope of this ring contraction reaction, we studied the reaction of 2-benzamido-4,5-dihydro-3-furancarboxitriles<sup>2)</sup> with sodium iodide. The reaction of 2-benzamido-4,5-dihydro-3-furancarboxitrile

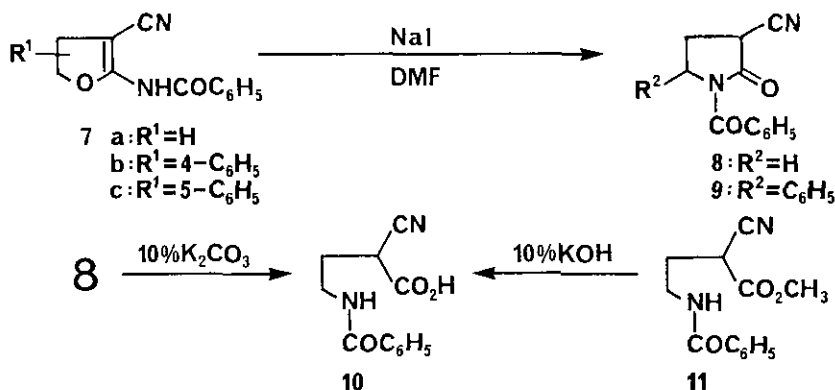
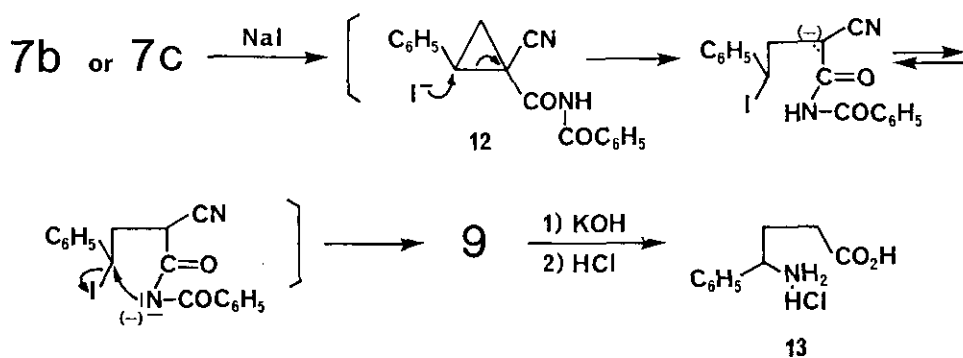


Chart 3

(7a) with sodium iodide (2 eq.) in DMF at 150°C for 1 h gave 1-benzoyl-2-oxo-3-pyrrolidinecarbonitrile (8) in 75% yield, no the expected cyclopropane derivative being isolated (Chart 3). On alkaline hydrolysis, 8 gave 4-benzamido-2-cyanobutanoic acid (10), which was identical with an authentic sample prepared from hydrolysis of methyl 4-benzamido-2-cyanobutanoate (11). Compound 11 was synthesized from methyl cyanoacetate and 1-benzoylaziridine according to the method of Stamm<sup>5)</sup>. The structure of 8 was supported by the above reaction and the analytical and spectral data<sup>6)</sup>. Finally, the reaction of 2-benzamido-4,5-dihydro-4-phenyl( or 5-phenyl)-3-furancarbonitrile [(7b) or (7c)] with sodium iodide resulted in the formation of the same product, 1-benzoyl-2-oxo-5-phenyl-3-pyrrolidinecarbonitrile (9).

In a similar manner, (E)-N-benzoyl-1-cyano-2-phenylcyclopropanecarboxamide (12)<sup>7)</sup> prepared from 1,2-dibromo-1-phenylethane and N-cyanoacetylbenzamide<sup>8)</sup> provided 9. These findings suggest that 7b and 7c underwent ring contraction to furnish 12, which was converted to the carbanion by iodide ion, and then the carbanion rearranged into the amido ion, which underwent intramolecular cyclization to form 9 (Chart 4). On treatment with hot 5% potassium hydroxide, and then with hot 35% hydrochloric acid, 9 underwent hydrolysis and decarboxylation to provide 4-amino-4-phenylbutanoic acid hydrochloride (13), which was identical with an authentic sample prepared from 4-amino-4-phenylbutanoic acid<sup>9)</sup> and hydrochloric acid. The structure assignment of 9 was based on the above reaction, the satisfactory elemental analysis and the spectral data<sup>10)</sup>. Further studies on the scope and limitation of the present reaction are now in progress.



## REFERENCES

- 1) R. Helmers, Angew. Chem., 1971, 83, 756.
- 2) T. Matsuda, K. Yamagata, Y. Tomioka, and M. Yamazaki, Chem. Pharm. Bull., 1985, 33, 937.
- 3) R. K. Singh and S. Danishefsky, J. Org. Chem., 1975, 40, 2969.
- 4) E. W. Yankee, B. Spencer, N. E. Howe, and D. J. Cram, J. Am. Chem. Soc., 1973, 95, 4220.
- 5) H. Stamm, L. Scheneider, and J. Budny, Chem. Ber., 1976, 109, 2005.
- 6) Colorless prisms, mp 144-145 °C (acetone-petr. benzin). Anal. Calcd for  $C_{12}H_{10}N_2O_2$ : C,67.28; H,4.71; N,13.08. Found: C,67.19; H,4.47; N,13.09. Ir (KBr) 2260 (CN), 1680 and 1755  $cm^{-1}$ (CO).  $^1H$  nmr ( $CDCl_3$ )  $\delta$ : 3.70 (1H, dd, J=10.0, 8.5Hz,  $C_3$ -H), 3.84-4.18 (2H, m,  $C_5$ -H), 2.27-2.63 (2H, m,  $C_3$ -H), 7.28-7.62 (5H, m, aromatic H).
- 7) Colorless columns, mp 135-136 °C (acetone-petr. benzin). Anal. Calcd for  $C_{18}H_{14}N_2O_2$ : C,74.47; H,4.86; N,9.65. Found: C,74.50; H,4.75; N,9.70. ir (KBr) 3430 (NH), 2230 (CN), 1755 and 1690  $cm^{-1}$ (CO).  $^1H$  Nmr ( $CDCl_3$ )  $\delta$ : 2.11-2.45 (2H, m,  $C_3$ -H), 3.34 (1H, t, J=8.5Hz,  $C_2$ -H), 7.30-7.64 (8H, m, aromatic H), 7.82-7.93 (2H, m, aromatic H), 9.43 (1H, br s, N-H). Compound 12 was hydrolyzed by hot 5% potassium carbonate to give (E)-1-cyano-2-phenylcyclopropane-carboxylic acid<sup>4)</sup>.
- 8) G. Shaw, J. Chem. Soc., 1955, 1834.
- 9) K. W. Rosenmund and P. Engels, Arch. Pharm., 1951, 284, 209.
- 10) Colorless needles, mp 249-249.5°C (DMF- $H_2O$ ). Anal. Calcd for  $C_{18}H_{14}N_2O_2$ : C,74.47; H,4.86; N,9.65. Found: C,74.44; H,4.77; N,9.45. Ir (KBr) 2260 (CN), 1680 and 1755  $cm^{-1}$ (CO).  $^1H$  Nmr [ $(CD_3)_3SO$ ]  $\delta$ : 4.52 (0.6H, dd, J=12.0, 8.5Hz,  $C_3$ -H), 4.78 (0.4H, t, J=10.0Hz,  $C_3$ -H), 2.75-3.05 (1H, m,  $C_4$ -H), 2.08-2.54 (1H, m,  $C_4$ -H), 5.24 (0.6H, dd, J=10.5, 6.5Hz,  $C_5$ -H), 5.59 (0.4H, dd, J=9.5, 3.5Hz,  $C_5$ -H), 7.21-7.92 (10H, m, aromatic H). Compound 9 seems to be a mixture of cis and trans isomers.

Received, 14th July, 1988