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

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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-pyrrolidinecarbonitrile (**8**).

Helmers[1] 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**)[2] 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**)][2] 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.

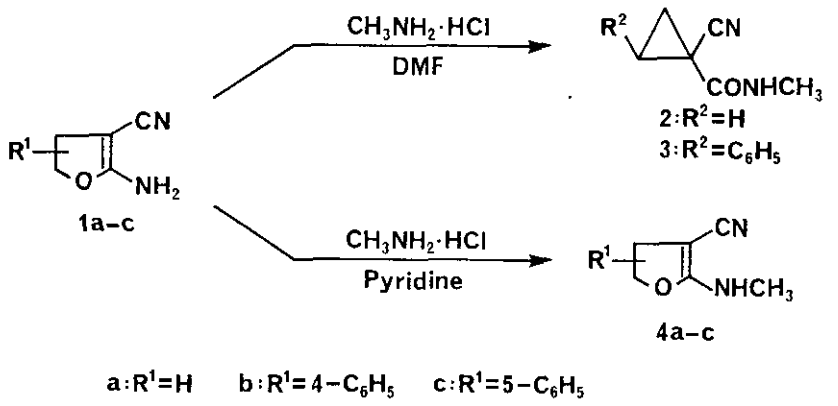


Chart 1

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[3] and (E)-1-cyano-2-phenylcyclopropanecarboxylic acid[4] 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.

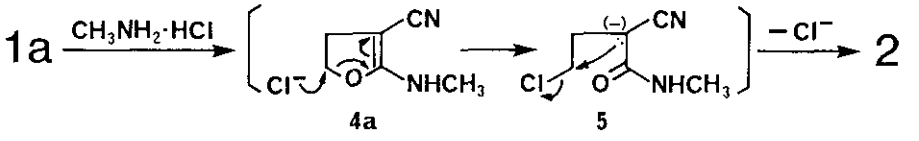


Chart 2

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.[4] mp 184-185 °C). The results are summarrized in Table. Sodium iodide was the most effective for the formation of **6**.

Table Reaction of **1b** with NaX

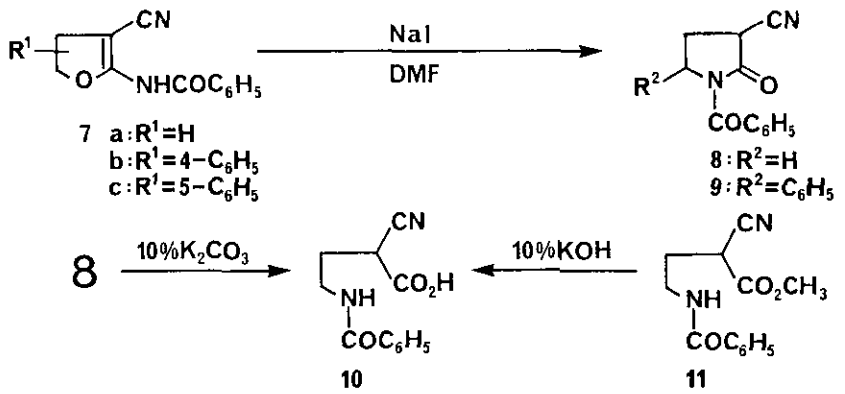
6

Exp. No.	NaX	Molar ratio NaX / **1b**	Solvent	Reaction conditions Temp(°C)	Time(h)	Yield of **6** (%)
1	NaI	2	DMF	120	9	62
2	NaBr	2	DMF	120	9	43
3	NaCl	2	DMF	120	9	7*)
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-furancarbonitrile (**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-furancarbonitriles[2] with sodium iodide. The reaction of 2-benzamido-4,5-dihydro-3-furancarbonitrile



7 a:R^1=H
b:R^1=4-C_6H_5
c:R^1=5-C_6H_5

8:R^2=H
9:R^2=C_6H_5

10 **11**

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[5]. The structure of **8** was supported by the above reaction and the analytical and spectral data[6]. 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-phenylcyclopropanecaboxamide (**12**)[7] prepared from 1,2-dibromo-1-phenylethane and N-cyanoacetylbenzamide[8] 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[9] and hydrochloric acid. The structure assignment of **9** was based on the above reaction, the satisfactory elemental analysis and the spectral data[10]. Further studies on the scope and limitation of the present reaction are now in progress.

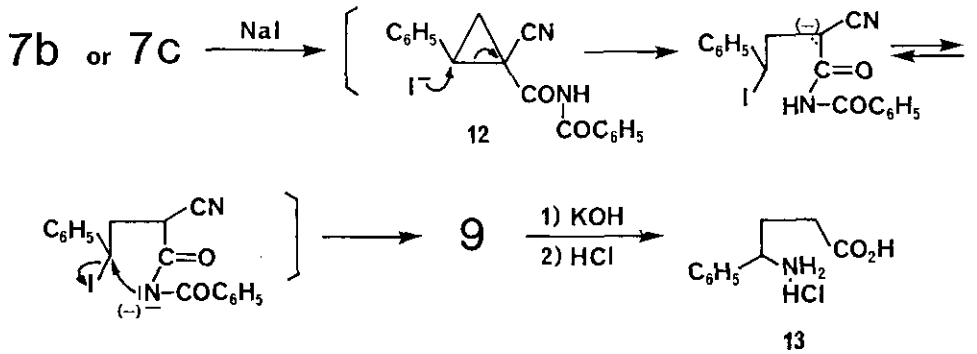


Chart 4

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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 ($CDCl_3$) δ : 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 ($CDCl_3$) δ : 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-phenylcyclopropanecarboxylic acid[4].

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 [$(CD_3)_3SO$] δ : 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.

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