SYNTHESIS OF 6-ALKYLAMINO-3-PYRIDAZINECARBOXYLIC ACID DERIVATIVES FROM METHYL 6-CHLORO-3-PYRIDAZINECARBOXYLATE

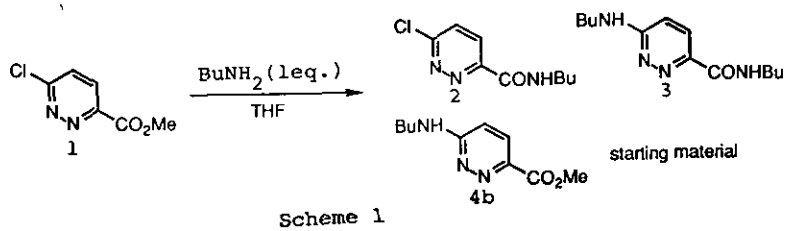
Shoetsu Konno, Mataichi Sagi, Futoshi Siga, and Hiroshi Yamanaka*

Pharmaceutical Institute, Tohoku University
Aobayama, Sendai 980, Japan

Abstract——The synthesis of methyl 6-alkylamino-3-pyridazinecarboxylates (**4a-c**) was accomplished by the following reaction sequence. On treatment of methyl 6-chloro-3-pyridazinecarboxylate (**1**) with methanolic ammonia, 6-chloro-3-pyridazinecarboxamide (**5**) was precipitated almost quantitatively, which reacted with primary alkylamines to give the corresponding 6-alkylamino-3-pyridazinecarboxamide (**6a-c**). These products were smoothly converted into the methyl esters (**4a-c**) by treatment with methanol in the presence of boron trifluoride etherate. The reaction of **1** with butylamine in THF gave a complicated mixture in which N-butyl-6-chloro-3-pyridazinecarboxamide(**2**), N-butyl-6-butylamino-3-pyridazinecalboxamide(**3**), **4b**, and **1** were involved.

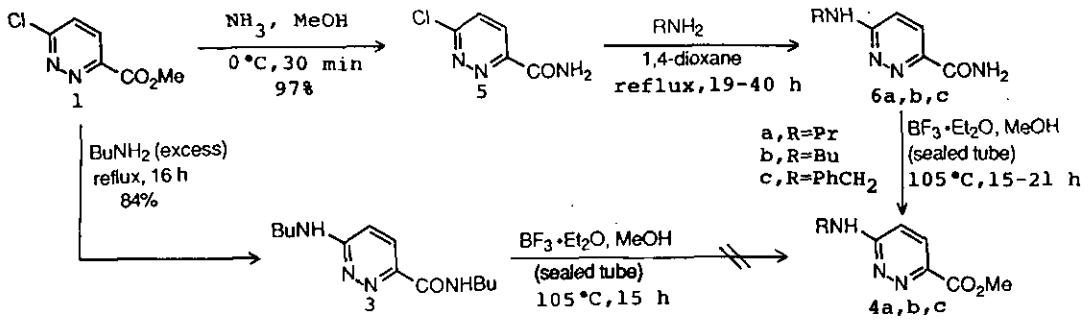
Concerning dopamine ß-hydroxylase inhibitory activity of 5-butyl-2-pyridinecarboxylic acid (Fusaric acid),[1] our interest was focussed on the synthesis of 6-substituted 3-pyridazinecarboxylic acids. During the investigation on the synthesis of these compounds, it was realized that the methoxycarbonyl group of methyl 6-chloro-3-pyridazinecarboxylate (**1**)[2] was more reactive toward N(nitrogen)-nucleophiles than the 6-chloro substituent.

When **1** (mp 147-149°C)[2] was heated with 1 mole eq. amount of butylamine in THF, a mixture of N-butyl-6-chloro-3-pyridazinecarboxamide (**2**), N-butyl-6-butylamino-3-pyridazinecarboxamide (**3**), methyl 6-butylamino-3-pyridazinecarboxylate (**4b**) and the starting material (**1**) was obtained. The yield of **4b** was so poor that the isolation of **4b** from the mixture was unsignificant.



Scheme 1

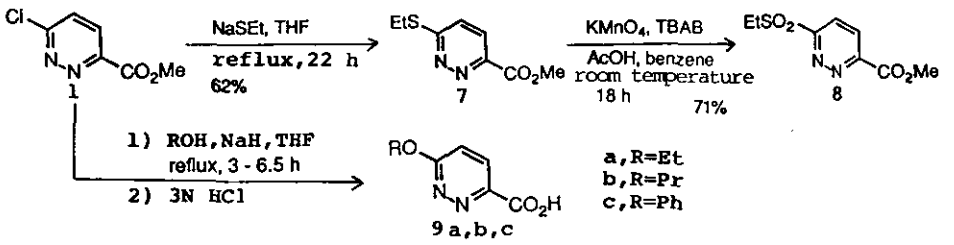
On the other hand, when **1** was treated with ammonia in methanol at 0°C for 0.5 h, 6-chloro-3-pyridazinecarboxamide (**5**), mp 243-244°C, was obtained in 97 % yield. The reaction of **5** with primary amines such as propylamine, butylamine, and benzylamine, in boiling 1,4-dioxane for 20-40 h yielded the corresponding 6-alkylamino-3-pyridazinecarboxamide (**6a**:R=Pr, mp 188-190°C; **6b**:R=Bu, mp 166-168 °C; **6c**:R=$PhCH_2$, mp 192-194°C) in satisfactory yields. On treatment with methanol in the presence of boron trifluoride etherate[3] (100-110°C in a sealed tube) for 15-21 h, **6a,b,c** were converted into methyl 6-alkylamino-3-pyridazinecarboxylate (**4a**:R=Pr, mp 138-140°C; **4b**:R=Bu, mp 119-121°C; **4c**:R=$PhCH_2$, mp 155-157°C) in 73-75 % yields. In connection with these findings, it was observed that the reaction of **1** with excess butylamine under stronger conditions (neat, reflux for 16 h) gave **3**, mp 121-123°C, in 84 % yield and that the methanolysis of **3** into **4b** failed under similar condition to those for the conversion (**6**→**4**). Accordingly, the reaction sequence from **1** to **4** via **5** and **6** is concluded to be practical for the synthesis of methyl 6-alkylamino-3-pyridazinecarboxylates (**4**).



Scheme 2

Furthermore, the reaction of **1** with 1.5 mole eq. amount of sodium ethanethiolate in boiling THF gave methyl 6-(ethylthio)-3-pyridazinecarboxylate (**7**), mp 129-131 °C, as a sole product. On treatment with potassium permanganate in acetic acid-benzene in the presence of tetrabutylammonium bromide[4] at room temperature, **7** was smoothly oxidized to give methyl 6-(ethylsulfonyl)-3-pyridazinecarboxylate

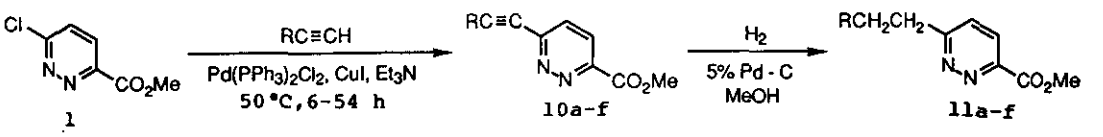
(**8**), mp 148-149°C. The reaction of **8** with 1 mole eq. amount of butylamine gave N-butyl-6-(ethylsulfonyl)-3-pyridazinecarboxamide, mp 133-134.5°C, in 44 % yield, and no **4b** was isolated.



Scheme 3

Unlike ethanethiolate anion, ethoxide ion seemed to attack the 3-methoxycarbonyl group of **1** predominantly. Namely, the reaction of **1** with ethanol in the presence of 5 mole eq. of amount of sodium hydride gave 6-ethoxy-3-pyridazinecarboxylic acid (**9a**), mp 130-132°C(decomp.), in 62 % yield, whereas no **9a** was isolated by use of 1 mole eq. amount of sodium hydride. Probably, 1 mole eq. amount of ethoxide ion was consumed for the formation of the ortho-acid type intermediate . Based on these findings, the 6-propoxy and 6-phenoxy derivatives (**9b,c**) were synthesized by use of excess sodium hydride directly from **1** in a form of free acid in 42-62 % yields.

Finally, it should be mentioned that the nickel catalyzed [$Ni(dppp)Cl_2$] cross-coupling reaction of **1** with Grignard reagents[5] resulted in the formation of resinous substance. The synthesis of methyl 6-alkyl-3-pyridazinecarboxylate (**11**) was achieved by palladium catalyzed [$PdCl_2(PPh_3)_2$] condensation of 1 with terminal acetylenes followed by the catalytic hydrogenation[6] of the resulting 6-alkynyl-3-esters (**10**). The Grignard reagents, like ethoxide ion, may attack the 3-methoxycarbonyl group preferentially, which disturbs the formation of the desired compounds. Thus, the synthesis of 6-benzyl-3-ester has not yet been achieved.



Scheme 4

Among the derivatives synthesized[7] through present investigation, 6-benzylamino-3-pyridazinecarboxylic acid was proved to have potent activity than Fusaric acid

for dopamine ß-hydroxylase inhibition in vitro. Biological data of all the compounds, together with further results on the synthesis, will be reported in the future.

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REFERENCES AND NOTES

1. H. Hidaka, T. Nagatsu, K. Takeya, H. Suda, K. Kojiri, M. Matsuzaki, and H. Umezawa, J. Antibiotics, 1969, **22**, 228.
2. The synthesis of **1** was easily achieved by the following procedure. The condensation of 2-oxoglutaric acid with hydrazine affored 6-oxo-1,4,5,6-tetrahydropyridazine-3-carboxylic acid. The oxidation of resulting tetrahydropyridazine followed by the esterification gave methyl 6-oxo-1,6-dihydro-3-pyridazinecarboxylate which was dehydroxy-chlorinated with phosphoryl chloride to give **1**. [R. C. Evans and F. Y. Wiselogle J. Am. Chem. Soc., 1945, **67**, 60; G. B. Barlin and Y. Yap, Aust. J. Chem., 1977, **30**, 2319]
3. D. J. Hamilton and M. J. Price, Chem. Commun., **1969**, 414.
4. S. Konno, M. Yokoyama, A. Kaite, I. Yamatsuta, S. Ogawa, M. Mizugaki, and H. Yamanaka, Chem. Pharm. Bull., 1982, **30**, 152.
5. K. Tamao, K. Sumitani, and M. Kumada., J. Am. Chem. Soc., 1972, **94**, 4374.
6. S. Konno, M. Shiraiwa, and H. Yamanaka, Chem. Pharm. Bull., 1981, **29**, 3554.
7. All the new compounds described in this paper showed satisfactory value for elemental analysis and ^{1}H-nmr and ir spectroscopy.

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