

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

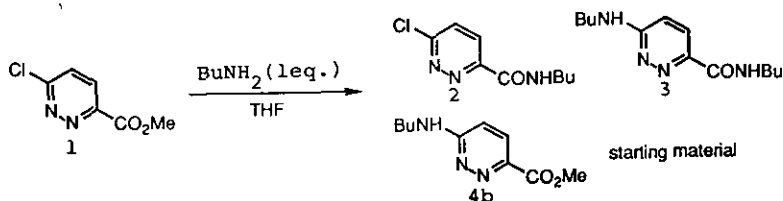
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Abstract—The synthesis of methyl 6-alkylamino-3-pyridazinecarboxylates (**4a-c**) was accomplished by the following reaction sequence. On treatment of methyl 6-chloro-3-pyridazinecarboxylate (**1**) with methanolic ammonia, 6-chloro-3-pyridazinecarboxamide (**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-pyridazinecarboxamide(**3**), **4b**, and **1** were involved.

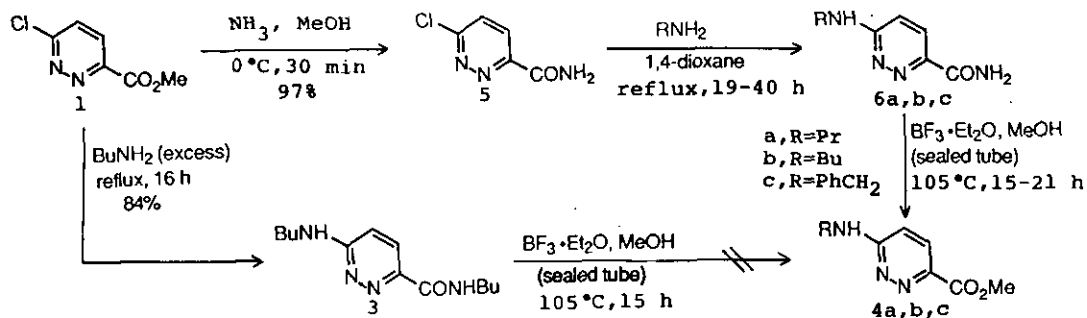
Concerning dopamine  $\beta$ -hydroxylase inhibitory activity of 5-butyl-2-pyridinecarboxylic acid (Fusaric acid),<sup>1</sup> our interest was focussed on the synthesis of 6-substituted 3-pyridazinecarboxylic acids. During the investigation on the synthesis of these compounds, it was realized that the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

When **1** (mp 147-149°C)<sup>2</sup> 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 insignificant.



Scheme 1

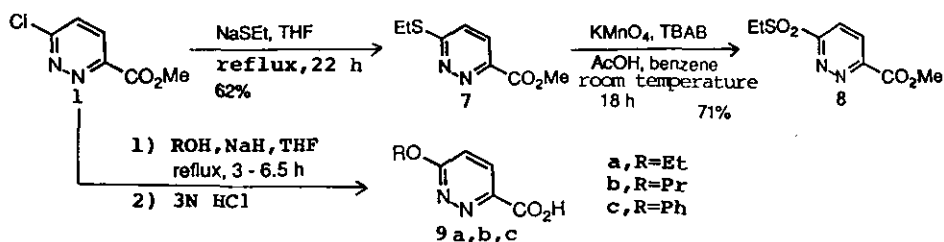
On the other hand, when 1 was treated with ammonia in methanol at  $0^\circ\text{C}$  for 0.5 h, 6-chloro-3-pyridazinecarboxamide (5), mp  $243\text{--}244^\circ\text{C}$ , was obtained in 97 % yield. The reaction of 5 with primary amines such as propylamine, butylamine, and benzylamine, in boiling 1,4-dioxane for 20-40 h yielded the corresponding 6-alkylamino-3-pyridazinecarboxamide (6a:R=Pr, mp  $188\text{--}190^\circ\text{C}$ ; 6b:R=Bu, mp  $166\text{--}168^\circ\text{C}$ ; 6c:R= $\text{PhCH}_2$ , mp  $192\text{--}194^\circ\text{C}$ ) in satisfactory yields. On treatment with methanol in the presence of boron trifluoride etherate<sup>3</sup> ( $100\text{--}110^\circ\text{C}$  in a sealed tube) for 15-21 h, 6a,b,c were converted into methyl 6-alkylamino-3-pyridazinecarboxylate (4a:R=Pr, mp  $138\text{--}140^\circ\text{C}$ ; 4b:R=Bu, mp  $119\text{--}121^\circ\text{C}$ ; 4c:R= $\text{PhCH}_2$ , mp  $155\text{--}157^\circ\text{C}$ ) 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  $121\text{--}123^\circ\text{C}$ , in 84 % yield and that the methanolysis of 3 into 4b failed under similar condition to those for the conversion (6 $\rightarrow$ 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  $129\text{--}131^\circ\text{C}$ , as a sole product. On treatment with potassium permanganate in acetic acid-benzene in the presence of tetrabutylammonium bromide<sup>4</sup> at room temperature, 7 was smoothly oxidized to give methyl 6-(ethylsulfonyl)-3-pyridazinecarboxylate

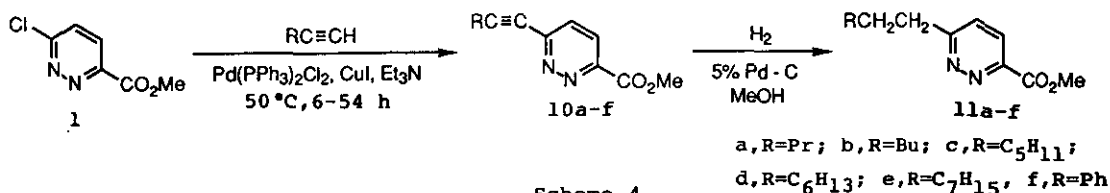
(8), mp 148-149°C. The reaction of 8 with 1 mole eq. amount of butylamine gave *N*-butyl-6-(ethylsulfonyl)-3-pyridazinecarboxamide, mp 133-134.5°C, in 44 % yield, and no 4b was isolated.



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  $[\text{Ni}(\text{dppp})\text{Cl}_2]$  cross-coupling reaction of 1 with Grignard reagents<sup>5</sup> resulted in the formation of resinous substance. The synthesis of methyl 6-alkyl-3-pyridazinecarboxylate (11) was achieved by palladium catalyzed  $[\text{PdCl}_2(\text{PPh}_3)_2]$  condensation of 1 with terminal acetylenes followed by the catalytic hydrogenation<sup>6</sup> 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<sup>7</sup> through present investigation, 6-benzylamino-3-pyridazinecarboxylic acid was proved to have potent activity than Fusaric acid

for dopamine  $\beta$ -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

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2. The synthesis of 1 was easily achieved by the following procedure. The condensation of 2-oxoglutaric acid with hydrazine afforded 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-pyridazine-carboxylate 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]
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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  $^1\text{H}$ -nmr and ir spectroscopy.

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