FACILE SYNTHESIS OF THIAZOLO[4,5-b]- AND THIENO[3,2-b]PYRIDINE DERIVATIVES BY A NOVEL PYRIDINE CYCLIZATION REACTION VIA ENAMINE INTERMEDIATES[1]

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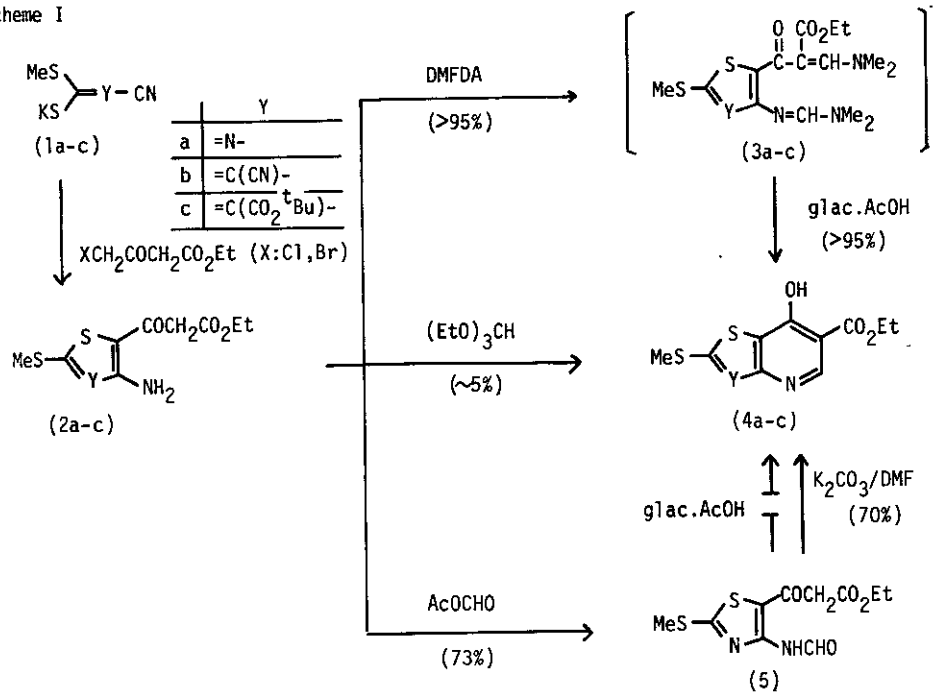
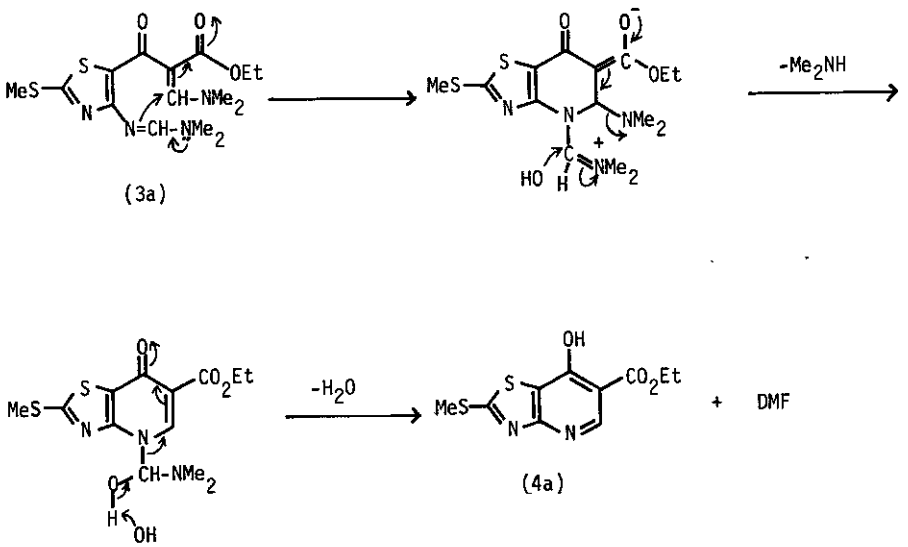
Abstract——Thiazolo[4,5-b]- and thieno[3,2-b]pyridine-6-carboxylic acid derivatives were synthesized by formation of the thiazole or the thiophene ring bearing o-amino-β-ketoester moiety, followed by a novel pyridine cyclization reaction with DMF-dimethylacetal.

In reaction of ethyl 4-haloacetoacetate with cyanamide (1a)[2] or malononitrile derivatives (1b)[3], we found that spontaneous cyclization took place to afford thiazole 2a[4] [73.2%, mp 92°C, NMR ($CDCl_3$) δ : 1.27 (3H, t, J=7.5 Hz, ester CH_3), 2.67 (3H, s, SCH_3), 3.59 (2H, s, $COCH_2CO_2$), 4.24 (2H, q, J=7.5 Hz, ester CH_2), 6.87 (2H, bs, NH_2, disappeared by D_2O)] or thiophene 2b[5] [73.2%, mp 152-153°C] bearing o-amino-β-ketoester moiety, respectively. Attempts to cyclize 2a by the conventional method[6] with triethyl orthoformate were unsuccessful and the desired thiazolo[4,5-b]pyridine (4a) was not practically obtained, probably because of weak basicity of the amino group of 2a. Consequently, the pyridine cyclization reaction was studied using more active DMF-dimethylacetal (DMFDA). Compound 2a was converted to the enamine derivative (3a) [$C_{15}H_{22}N_4O_3S_2$, ∿ 100%, mp 169-170°C. NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7.0 Hz, ester CH_3), 2.54 (3H, s, SCH_3), 2.79 and 2.93 (each 6H, s, $N(CH_3)_2$), 3.86 (2H, q, J=7.0 Hz, ester CH_2), 7.32 (1H, s, N=CH-N), 8.30 (1H, s, C=CH-N)], which was then treated with glc. acetic acid at room temperature to afford the desired cyclized product (4a) [mp 198-199°C, NMR ($CDCl_3$ + CF_3CO_2H (2 drops)) δ : 1.42 (3H, t, J=7.5 Hz, ester CH_3), 2.91 (3H, s, SCH_3), 4.53 (2H, q, J=7.5 Hz, ester CH_2), 8.99 (1H, s, C_5-H)], almost quantitatively. This synthetic route was achieved in one-pot system in good yield. Moreover, this cyclization reaction unexpectedly occurred in applying 3a to silica gel column chromatography using chloroform as an eluent to give not only 4a but DMF simultaneously. The mechanism of the pyridine cyclization reaction was then considered. As shown in Scheme II, we postulate that this pyridine cyclization is a new reaction in the point that C_1-unit of the 2-position of pyridine ring is derived from the enamino-carbon attached to the active methylene of β-ketoester moiety.

Scheme I

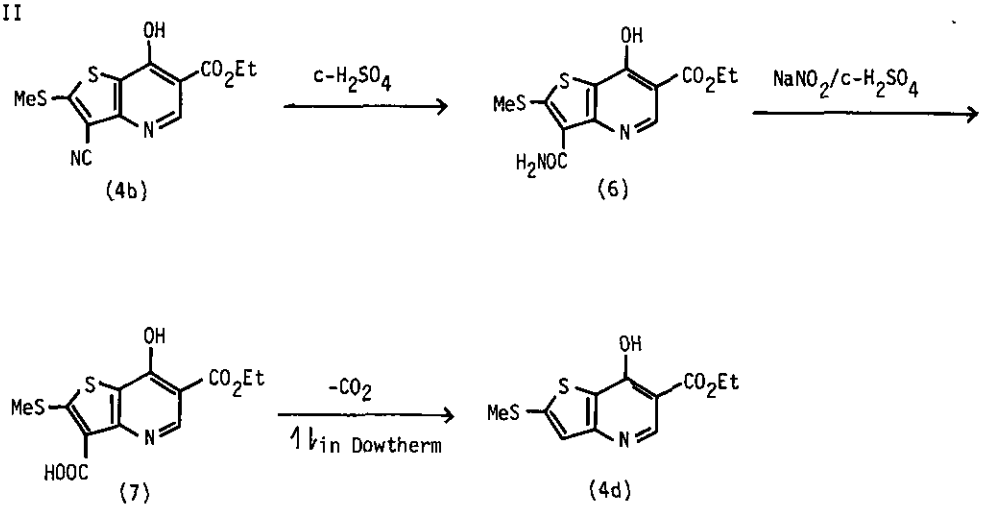


Scheme II



This postulation was further confirmed by the facts that the enamine intermediate (3a) was not converted to 4a under basic conditions adopted by modified method of Camps' quinoline synthesis[7] and that, on the contrary, the formamide derivative (5) [73.0%, 100-102°C. IR ν_{max}^{KBr} cm^{-1} : 3370, 1720, 1700, 1610. NMR ($CDCl_3$) δ : 1.30 (3H, t, J=7.0 Hz, ester CH_3), 2.78 (3H, s, SCH_3), 3.70 (2H, s, $COCH_2CO_2$), 4.27 (2H, q, J=7.0 Hz, ester CH_2), 9.55 (1H, d, J=10.5 Hz, CHO, change into s by D_2O), 10.20 (1H, bd, J=10.5 Hz, NH, disappeared by D_2O)], obtained by formylation of 2a with acetic formic anhydride, was cyclized to give 4a only under the same basic condition and not in glc. acetic acid. In addition, thieno[3,2-b]pyridine (4b) [~100% from 2b, mp 243-244°C. NMR ($CDCl_3$ + CF_3CO_2H (2 drops)) δ : 1.47 (3H, t, J=7.5 Hz, ester CH_3), 2.92 (3H, s, SCH_3), 4.57 (2H, q, J=7.5 Hz, ester CH_2), 9.09 (1H, s, C_5-H)] was easily obtained in excellent yield from 1b through the same synthetic route as for 4a. Compound 4d [64.5%, 253-256°C. NMR ($CDCl_3$ + CF_3CO_2H (2 drops)) δ : 1.46 (3H, t, J=7.5 Hz, ester CH_3), 2.91 (3H, s, SCH_3), 4.56 (2H, q, J=7.5 Hz, ester CH_2), 7.42 (1H, s, C_3-H), 9.03 (1H, s, C_5-H)], corresponding to the carba-analogue of 4a, was prepared according to the synthetic method as shown in Scheme III.

Scheme III



By treating 4b with conc. sulfuric acid at room temperature to hydrate the cyano group to the amide and then by adding sodium nitrite[8] in conc. sulfuric acid at 40-60°C to hydrolyze selectively the amido group, the carboxylic acid (7) [63.0%, mp 279-280°C. NMR ($CDCl_3$ + CF_3CO_2H (2 drops)) δ : 1.47 (2H, t, J=7.5 Hz, ester CH_3), 3.09 (3H, s, SCH_3), 4.21 (2H, q, J=7.5 Hz, ester CH_2), 7.3-8.0 (2H, bs, $CONH_2$), 9.21 (1H, s, C_5-H)] was obtained. This carboxylic acid (7) yielded compound 4d by decarboxylation in refluxing Dowtherm. Compound 4c [83% from 2c, mp 197-198°C. NMR ($CDCl_3$ + CF_3CO_2H (1 drop)) δ : 1.46 (3H, t, J=7.5 Hz, ester CH_3), 2.81 (3H, s, SCH_3), 4.56 (2H, q, J=7.5 Hz, ester

CH_2), 9.03 (1H, s, C_5-H)], obtained by a similar manner as shown in Scheme I using tert-butyl cyanoacetate instead of malononitrile as a starting material, was led to 7 almost quantitatively by selective hydrolysis in trifluoroacetic acid at room temperature or in refluxing glc. acetic acid.

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