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A NEW USE OF THE VILSMEIER-HAACK REAGENT. SYNTHESIS OF 9-DEAZAPURINE DERIVATIVES

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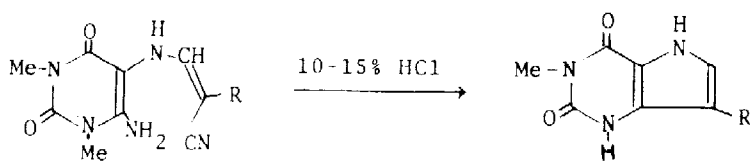
Many 9-deazapurine derivatives (5H-pyrrolo[3,2-d]pyrimidines) have been synthesized from pyrimidine derivatives as antimetabolites or chemotherapeutic agents,[1,2,3] because the ring system is isomeric with that of naturally occurring purines and indoles. Recently, we have also synthesized 2,3,4,5-tetrahydro-3-methyl-2,4-dioxo-1H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile (2a) from the reaction of 6-amino-5-(2,2-dicyanovinyl)amino-1,3-dimethyluracil (1a) with 15% HCl (Chart 1).[4] Compound (2a) might be regarded as a useful starting material to prepare its derivatives, since it has a nitrile at 7-position and a hydroxyl group (or carbonyl) at 2-position. For example, the nitrile was easily hydrolyzed to an amide group (8a) after treatment with conc. H_2SO_4. Chlorination of a hydroxyl group was reported by Imai,[5] where such compounds as (2a) were refluxed in $POCl_3$. However, no reaction occurred when (2a) was refluxed in $POCl_3$. The reason is probably due to the solubility of (2a), which is insoluble in hot $POCl_3$ (also slightly soluble in hot methanol, ethanol, acetonitrile, dichloromethane and dimethylsulfoxide).

In contrast, compound (2a) reacted actively with $POCl_3$-DMF (dimethylformamide), known as the Vilsmeier-Haack reagent,[6] to give a brown solution, which was heated on a water bath for 1 hr and the solvent was evaporated under a reduced pressure. The residue was washed with dry dichloromethane to give



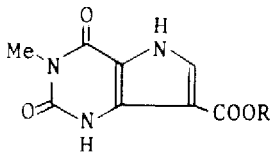
(1a) R=CN
(1b) R=COOEt

(2a) R=CN
(2b) R=COOEt

Chart 1

Table I

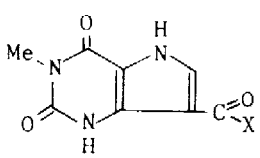
2,3,4,5-Tetrahydro-2,4-dioxo-1H-pyrrolo[3,2-d]pyrimidine-7-carboxylates



No	R	Yield (%)	mp (°C)
6a	H	40	>300
6b	CH_3	45	> 260
6c (=2b)	C_2H_5	67	266-267
6d	n-C_3H_7	68	> 300
6e	C_6H_5-CH_2	51	282-283

Table II

2,3,4,5-Tetrahydro-2,4-dioxo-1H-pyrrolo[3,2-d]pyrimidine-7-carboxamide and Its Derivatives



No	X	Yield (%)	mp(°C)
8a	-NH_2	54	>300
8b	-NH-C_6H_5	54	>300
8c	-N⟨ ⟩	65	283-284

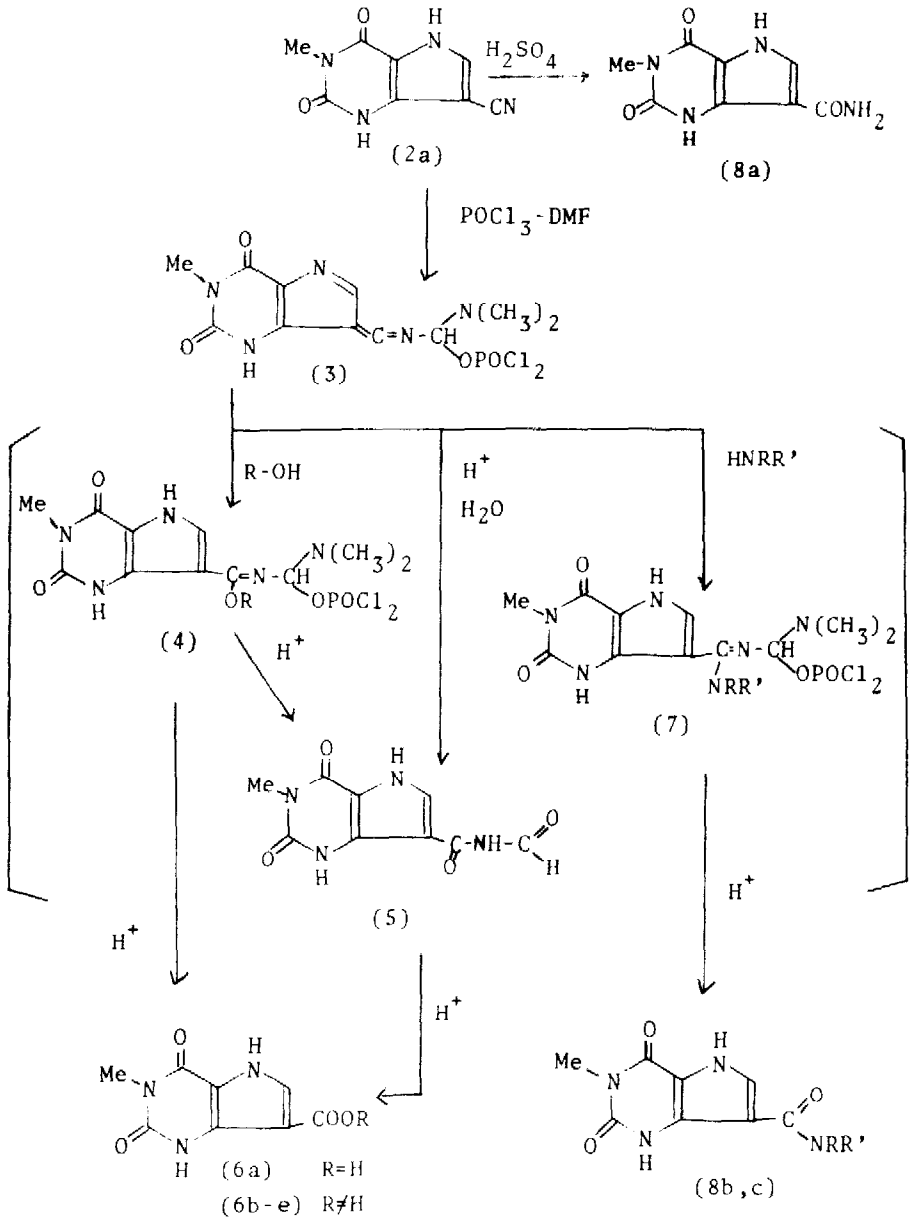


Chart 2

a crude hygroscopic gum (3). Ethanolysis, followed by hydrolysis of this intermediate (3) gave ethyl 2,3,4,5-tetrahydro-3-methyl-2,4-dioxo-1H-pyrrolo-[3,2-d]pyrimidine-7-carboxylate (6c or 2b) which has already been synthesized from 6-amino-5-(2-cyano-2-ethoxycarbonyl)amino-1,3-dimethyluracil (1b).[4]

Other ester derivatives, such as methyl, n-propyl and benzyl, were obtained by a similar method. On treatment with water, the intermediate (3) was converted to a carboxylic acid (6a) via an intermediate (5) which was checked by a mass-analysis (M^+=236), while the treatment of (3) with amines, followed by hydrolysis, afforded amide derivatives (8b,c). These results are listed in Table I and II.[7]

We suggest a mechanism, as shown in Chart 2, where a proton shift in pyrrole ring NH, followed by reaction with $POCl_3$-DMF probably gives a ketenimine (3). The reaction of the ketenimine with alcohol, water or amine might give the corresponding imino ether (4, R≠H), imidic acid (4, R=H) or amidine (7), which is easily hydrolyzed respectively to ester (6b-e), carboxylic acid (6a) and amide (8b,c). It should be noted that conversion of (3) to (6b-e) was easily carried out without adding diluted HCl after the reaction with alcohols, whereas conversion of (3) to (8b,c) needed the acid. This difference might be due to the stability of the intermediates (4), (5) and (7) against hydrolysis.

In conclusion, it is worth noting that nitrile conjugated with an enamine system in compound (2a) easily reacted with the Vilsmeier-Haack reagent to give the reactive key-intermediate (3). This might be a new use of the reagent in organic synthesis.

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7) Satisfactory analytical data were obtained for all derivatives.