STUDIES ON PYRIMIDINE DERIVATIVES. XVII[1]. SYNTHESIS OF PYRIMIDINE-4-CARBOXYLIC ESTERS

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Abstract—— During the controlled oxidation of polymethylpyrimidines with selenium dioxide in pyridine, it was observed that the 4-methyl group on the pyrimidine ring was selectively oxidized to give pyrimidine-4-carboxylic acids. In addition to this investigation, the transformation of pyrimidinecarboxamides into methyl pyrimidinecarboxylates was successfully achieved in methanol in the presence of boron trifluoride etherate.

Although the oxidation of 4,6-dimethylpyrimidine with a limited amount of potassium permanganate was reported to give 6-methylpyrimidine-4-carboxylic acid[2], few studies of the oxidation of polymethylpyrimidines as a preparative route to pyrimidinecarboxylic acids have been undertaken. From this point of view, we examined the reaction of polymethylpyrimidines with a limited amount of selenium dioxide and found site-selective formation of pyrimidine-4-carboxylic acids from such substrates. The present paper deals with this oxidation and also with the conversion of pyrimidinecarboxamides into methyl pyrimidinecarboxylates, carried out as a preparation of authentic specimens.

A typical procedure for the oxidation is as follows. A slight excess of selenium dioxide (95 % pure, 2.8 g, 0.024 mole) was added to a pyridine solution (30 ml) of 2,4-dimethylpyrimidine (Id)(2.16 g, 0.02 mole) and the mixture was refluxed for 5 hr. After the precipitated selenium had been removed by filtration, 3N NaOH (10 ml) was added to the filtrate. The mixture was evaporated under reduced pressure, H_2O was added to the residue and the mixture again evaporated under reduced pressure to remove the pyridine completely. The residue was dissolved in H_2O and the solution was washed with CH_2Cl_2. 3N HCl (10 ml) was added to the aqueous solution which was then evaporated to dryness under reduced pressure. The residue was dis-

solved in methanol (30 ml) containing $SOCl_2$ (3 ml) and the mixture was allowed to stand at room temperature for 10 hr. Usual work-up afforded methyl 2-methylpyrimidine-4-carboxylate (IVd), bp 115-125° (19 mmHg), mp 54-55° (Et_2O-hexane), in an overall yield of 65 %(1.98 g). Gas chromatographic analysis showed the absence of the 2-isomer and the diester in the product. Similar results were obtained for other dimethyl- or trimethyl-pyrimidines and these are summerized in Table I and II. As shown in Table I, 4,6-dimethyl derivatives gave pyrimidine-monocarboxylic acids as the main products with pyrimidine-dicarboxylic acids as minor ones.

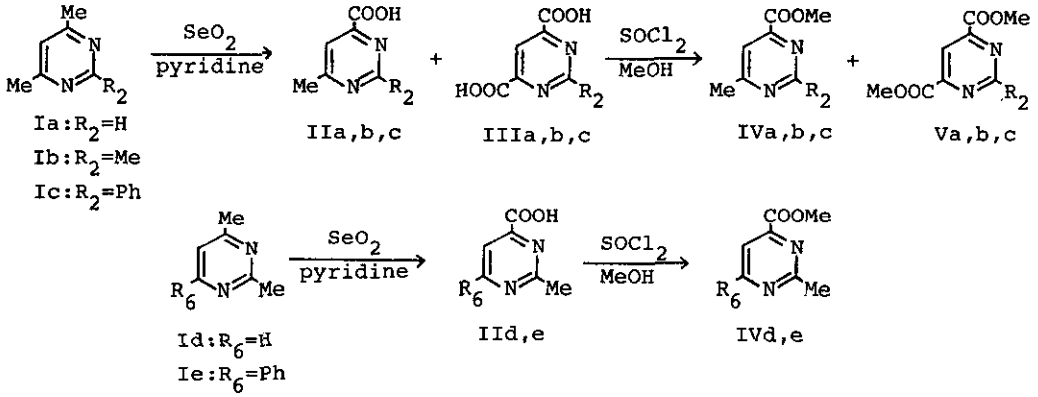


Table I. Yields, Melting Points, and Spectral Data of IVa-e

	Yield* (%)	mp(°C)	IR cm^{-1} ($CHCl_3$)	NMR($CDCl_3$)ppm -Me	-OMe	ring proton
IVa	29	66-68	1738	2.64(3H,s)	4.01(3H,s)	7.91(1H,s) 9.27(1H,s)
IVb	26	53-55	1733	2.62(3H,s) 2.82(3H,s)	4.03(3H,s)	7.68(1H,s)
IVc	40	102-103	1730	2.63(3H,s)	4.00(3H,s)	7.67(1H,s)
IVd	65	54-55	1739	2.85(3H,s)	4.02(3H,s)	7.82(1H,d,J=5.0Hz) 8.90(1H,d,J=5.0Hz)
IVe	58	91-93	1733	2.85(3H,s)	4.00(3H,s)	8.20(1H,s)

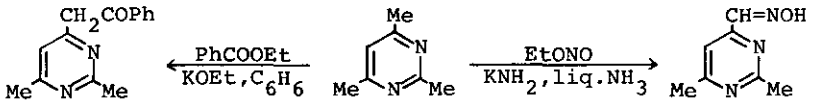
*) Over-all yields from I are recorded.

Table II. Yields, Melting Points, and Spectral Data of Va-c

	Yield* (%)	mp(°C)	IR cm^{-1} ($CHCl_3$)	NMR($CDCl_3$)ppm -Me	-OMe	ring proton
Va	11	81-82	1745		4.10(6H,s)	8.63(1H,s) 9.53(1H,s)
Vb	7	150-152	1740	2.98(3H,s)	4.10(6H,s)	8.47(1H,s)
Vc	7	163.5-164.5	1742		4.05(6H,s)	8.45(1H,s)

*) Over-all yields from I are recorded.

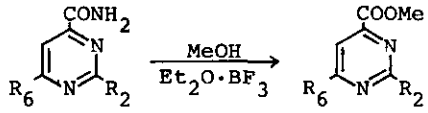
During investigation of the synthesis of pyrimidine derivatives starting from polymethylpyrimidines, superior reactivity of a 4-methyl group to a 2-methyl group in the same molecule was generally found. For example, 2,4,6-trimethylpyrimidine (Ib) reacted with ethyl nitrite in liquid ammonia to give 2,6-dimethylpyrimidine-4-aldoxime without formation of the 2-aldoxime[3]. Acylation of Ib with ethyl benzoate in the presence of potassium ethoxide is also known to give the 4-phenacyl derivative, selectively[4-6]. This relative reactivity of the two methyl groups was also observed in the selenium dioxide oxidation of polymethylpyrimidines described above.



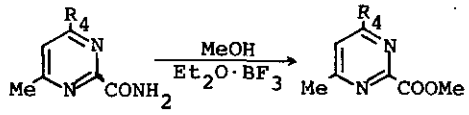
VII Ib VI

In order to confirm selective oxidation on the 4-methyl group authentic specimens of the esters (IV) were prepared from the corresponding amides which were unequivocally prepared by the controlled hydrolysis of cyanopyrimidines[7,8] or by homolytic amidation of disubstituted pyrimidines[9]. Namely, pyrimidine-4-carboxamides were heated in methanol in the presence of boron trifluoride etherate to give the esters in good yields.

Methyl 2-methyl-6-phenylpyrimidine-4-carboxylate, mp 91-93° (hexane), thus obtained from 2-methyl-6-phenylpyrimidine-4-carboxamide, was identical with IVe in every respect. Since the methanolysis of pyrimidinecarboxamides to the corresponding esters has not been reported the results of this amide-ester conversion are summarized below, including data for the pyrimidine-2-carboxylates.



IVc: R_2=Ph, R_6=Me 65 %
IVe: R_2=Me, R_6=Ph 94 %



VIIIa: R_4=Me
VIIIb: R_4=Ph

	Yield (%)	mp or bp(mmHg) (°C)	IR cm^{-1} ($CHCl_3$)	NMR($CDCl_3$)ppm -Me	-OMe	ring proton
VIIIa	20	150-155(16)[7]	1743	2.60(6H,s)	4.04(3H,s)	7.25(1H,s)
VIIIb	46	85-89	1735	2.67(3H,s)	4.04(3H,s)	7.68(1H,s)

Since the availability of pyrimidine-2- and -4-carboxylic esters had been restricted prior to the present work, the experiments described above should enable the ready preparation of these compounds.

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