PYRIMIDINES

XXXI.* PREPARATION OF 4(6)-SUBSTITUTED 2-FLUOROPYRIMIDINES

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The preparation of 4(6)-substituted 2-fluoropyrimidines by the action of cesium fluoride on the corresponding 2-chloropyrimidines in aprotic dipolar solvents is described. Spectral data confirming the structures of the fluoropyrimidines obtained are presented.

Halopyrimidines are widely used to obtain diverse functional derivatives of pyrimidine. Fluoropyrimidines are of considerable interest as heteroarylating compounds, since they are the most reactive halopyrimidines. Polysubstituted fluoropyrimidines are relatively accessible and consequently have received the most study; disubstituted fluoropyrimidines have been studied to a much lesser extent, and there is no information at all regarding unsubstituted monofluoropyrimidines, despite the attempts made to synthesize them, particularly in the synthesis of 2-fluoropyrimidine [2,3].

We have undertaken research to obtain 2-fluoropyrimidine (I) and its 4(6)-substituted derivatives (II-X) in order to study their reactivities and to ascertain the effect of the nature of the substituent on the lability of the fluorine atom in nucleophilic substitution reactions.

The introduction of fluorine atoms into the electron-deficient even-numbered positions of the pyrimidine ring is usually accomplished by replacement of chlorine atoms or a trimethylammonium group by fluorine by the action of sulfur tetrafluoride or alkali metal fluorides [4-6]. To obtain I-X, we selected a method involving replacement of chlorine atoms by fluorine in the corresponding chloropyrimidines. The use of cesium fluoride as the fluorinating agent and carrying out the reaction in aprotic dipolar solvents, as is well known [4,6-8], make it possible to considerably lower the reaction temperature and shorten the reaction time. Satisfaction of the indicated conditions is essential for the preparation of reactive monofluoropyrimidines, in which, according to our observations, the thermal stability is lower and the capacity for self-quaternization is higher than for polyfluoropyrimidines (the latter can be obtained by reaction of the corresponding chloropyrimidines and potassium fluoride at high temperatures in the absence of solvents [9, 10]). The reaction conditions and yields of the fluoropyrimidines obtained by us and their physical constants and analytical data are presented in Table 1. When liquid fluoropyrimidines are obtained, it is usually preferable to use N-methyl-α-pyrrolidone (MAP) as the solvent rather than dimethylformamide (DMF), in which impurities that are difficult to separate from the major product are formed; dimethylformamide can be used as the solvent when relatively high-melting fluoropyrimidines are obtained.

The structures of I-VIII were confirmed by spectral data (Table 2). The previously noted [8] similarity between the UV spectra of the fluoro derivatives and the corresponding chloro derivatives, with a small bathochromic shift of the absorption bands of the latter, is observed on comparing the spectra of 2-fluoro- and 2-chloropyrimidines. Bands of variable intensity from the C–F valence vibrations at 1030-1125 cm^{-1} [12, 13] and intense bands of the skeletal vibrations of the fluorinated pyrimidine ring at 1370-1430 cm^{-1} [12-14] are observed in the IR spectra of I-VIII. The singlet characteristic for the fluorine atom in the 2 position of the pyrimidine ring [14-16] is observed at weak field (116-120 ppm from the signal of hexafluorobenzene) in the F^{19} NMR spectra; the signal is broadened due to quadrupole interaction with the

*See [1] for communication XXX.

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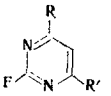
TABLE 1. 4(6)-Substituted 2-Fluoropyrimidines



Comp.	R	R′	Solvent	Reaction time, h	mp, °C	bp, °C (mm)	n_D^{25}
I	H	H	MAP	3,5	22—24	85—86 (135)	1,4623
II	CH_3	H	MAP	5	—	67—68 (120)	1,4643
III	CH_3	CH_3	DMF	7	12—14	74,5—75,5 (18)	1,4665
IV	C_6H_5	H	DMF	7	55—57	125—126 (3)	—
V	CH_3	C_6H_5	DMF	4,5	95—96,5	—	—
VI	C_6H_5	C_6H_5	DMF	6	94—96	—	—
VII	CH_3O	H	MAP	5	—	76—79 (135)	1,4730
VIII	$N(CH_3)_2$	H	DMF	40	63—64	—	
IX	F	H	MAP	6	—	68—70 (135); 53 (45)[11]	1,4290; 1,4278[11]
X	F	F	DMF	2,5	—	98,5—99; 98—99[9]	1,4025; 1,4038*[9]

Comp.	Empirical formula†	Found, %				Calc., %				Yield, %
		C	H	F	N	C	H	F	N	
I	$C_4H_3FN_2$	49,0	3,0	19,3	28,9	49,0	3,1	19,4	28,5	33
II	$C_5H_5FN_2$	53,2	4,2	16,5	24,7	53,6	4,5	16,9	25,0	16
III	$C_6H_7FN_2$	56,8	5,6	14,9	21,9	57,1	5,6	15,1	22,2	33
IV	$C_{10}H_7FN_2$	68,7	4,1	10,7	16,2	69,0	4,0	10,9	16,1	30
V	$C_{11}H_9FN_2$	70,1	4,8	9,9	14,8	70,2	4,8	10,1	14,9	30
VI	$C_{16}H_{11}FN_2$	76,8	4,5	7,4	11,3	76,8	4,4	7,6	11,2	36
VII	$C_5H_5FN_2O$	47,4	3,8	14,6	21,7	46,9	3,9	14,8	21,9	25
VIII	$C_6H_8FN_3$	50,8	5,8	13,2	29,5	51,0	5,7	13,5	29,8	80
IX	—	—	—	—	—	—	—	—	—	30
X	—	—	—	—	—	—	—	—	—	53

*At 20°.

† The molecular weights determined by mass spectrometry were in agreement with the calculated values.

TABLE 2. Data from the Spectra of 2-Fluoropyrimidines

Comp.	UV spectrum, λ max, nm (log ε)	NMR spectrum, chemical shift, ppm†			
		2-F	4-H	5-H	6-H
I	245 (3,57)	−118,7	8,69	7,30	8,69
II	248 (3,71)	−117,7	(2,51)	7,05	8,59
III	251 (3,77)	−116,1	(2,44)	6,91	(2,44)
IV	251 (3,85), 283 (4,25)	−118,5	(7,31—7,72, 7,99—8,26)	†	8,61
V	254 (3,25), 282 (4,27)	−117,0	(2,52)	‡	(7,31—7,61, 7,92—8,22)
VI	248 (4,41), 311 (4,48)	−117,9	(7,34—7,56, 7,99—8,21)	7,89	(7,34—7,56, 7,99—8,21)
VII	247 (3,70)	−120,5	(3,99)	6,61	8,28
VIII	239 (4,20), 284 (3,88)	−117,5	(3,09)	6,41	7,95

*From the signals of C_6F_6 and $(CH_3)_4Si$. The chemical shifts of the substituent protons are presented in parentheses.

† Coincides with the multiplet of the phenyl group at 7.31-7.72 ppm.

‡ Coincides with the multiplet of the phenyl group at 7.31-7.61 ppm.

adjacent nitrogen atom. The positions, multiplicities, and integral intensities of the proton signals in the H^1 NMR spectra are in complete agreement with the 4(6)-substituted 2-fluoropyrimidine structures (Table 2). More detailed data on the NMR spectra will be discussed in a separate paper.

EXPERIMENTAL

The UV spectra of ethanol solutions of the compounds obtained were recorded with a Unicam SP-700C recording spectrophotometer. The IR spectra of 5% solutions in CCl_4 were recorded with a UR-20 spectrometer. The H^1 and F^{19} NMR spectra of 5% solutions in CCl_4 were recorded at 38-39° with a Varian A 56/60 A spectrometer; hexamethyldisiloxane and hexafluorobenzene were used as internal standards.

Prior to the experiments, cesium fluoride was calcined at 440° for 7 h. The solvents (DMF and MAP) were dried over phosphorus pentoxide and distilled before the experiments. The starting chloropyrimidines were obtained by known methods.

Reaction of Chloropyrimidines with Cesium Fluoride. A mixture of 0.05 mole of chloropyrimidine, 0.15 mole of cesium fluoride, and 10 ml of MAP or 10-30 ml of DMF (depending on the solubility of the chloropyrimidine) was stirred at 150° for the period indicated in Table 1. Cesium fluoride was used in 0.2 mole and 0.3 mole amounts, respectively, in the reactions with dichloro- and trichloropyrimidines. In the case of II, the reaction mixture was stirred at 120°.

The reaction mixtures were worked up and the fluoropyrimidines were isolated by different methods depending on their properties.

Isolation of the Fluoropyrimidines

2-Fluoropyrimidine (I), 2,4-Difluoropyrimidine (IX), 2-Fluoro-4-methylpyrimidine (II), 2-Fluoro-4,6-dimethylpyrimidine (III), and 2-Fluoro-4-methoxypyrimidine (VII). The reaction mixture was treated with absolute ether, and the precipitate was removed by filtration and washed with ether. The ether was carefully removed by distillation at atmospheric pressure, and the residue was vacuum distilled, with collection of the entire fraction up to the start of distillation of the solvent. The distillation was repeated two to three times with collection each time of a fraction over a narrower interval. The last time, the fluoropyrimidines were distilled and collected over the intervals indicated in Table 1. According to gas-liquid chromatography (GLC), VII contained less than 2% impurities, while the remaining products contained less than 1% impurities.

2-Fluoro-4-phenylpyrimidine (IV). The reaction mixture was treated with absolute ether, and the precipitate was removed by filtration and washed with ether. The ether was removed by distillation, and the residue was vacuum-distilled. The collected product was recrystallized from petroleum ether (bp 40-60°).

2-Fluoro-4-methyl-6-phenylpyrimidine (V). The reaction mixture was worked up as in the case of IV. The residue after removal of the ether by distillation was dissolved in CCl_4, the solution was passed through activity II Al_2O_3, and the eluate was evaporated to dryness. The residue was sublimed at 100° (10 mm).

2-Fluoro-4,6-diphenylpyrimidine (VI). The reaction mixture was treated with four 25-ml portions of absolute benzene and filtered. The filtrate was evaporated and treated with 50 ml of water, and the precipitate was removed by filtration and refluxed in 60 ml of alcohol. The filtered alcohol solution was evaporated, and the residue was recrystallized from alcohol. The bis(4,6-diphenyl-2-pyrimidyl) oxide,* which was insoluble in boiling alcohol, was separated and recrystallized from acetic acid to give 3% of a product with mp 216-217°. Found: C 80.8; H 4.6; N 11.8%; mol. wt. 478. $C_{32}H_{22}N_4O$. Calculated: C 80.4; H 4.6; N 11.7%; mol. wt. 478. PMR spectrum (5% solution in $CDCl_3$), ppm: 7.88, singlet (pyrimidine 5-H), 7.21-7.49 and 7.90-8.14, multiplets (phenyl group protons).

2-Fluoro-4-dimethylaminopyrimidine (VIII). The reaction mixture was treated with 125 ml of water and extracted with benzene. The benzene extract was dried over magnesium sulfate and vacuum-evaporated, and the viscous residue was triturated with petroleum ether (bp 40-60°). The crystalline product was separated and recrystallized from petroleum ether.

*The formation of a side product of similar structure was noted in the preparation of 2,4-dinitrochlorobenzene [17].

2,4,6-Trifluoropyrimidine (X). The product was distilled from the reaction mixture with collection of a fraction up to bp 150°. A fraction with bp 98-100° was selected during redistillation. This material was redistilled with collection of a fraction with bp 98.5-99° (according to GLC, the amount of impurities in the product did not exceed 1%).

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