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FLUORINATED HETEROCYCLIC COMPOUNDS: SELECTIVE CHLORINE/FLUORINE EXCHANGE REACTIONS ON PYRIDAZINES

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SUMMARY

This work describes selective chlorine/fluorine substitution reactions on tetrachloropyridazine. Sodium fluoride, potassium fluoride and hydrogen fluoride were used as the fluorinating agents. It was found that sodium fluoride and potassium fluoride in the first fluorinating stage produce an exclusive substitution by fluorine of the chlorine bound in the 3-position. Difluorination and trifluorination produce mixtures of the three possible difluorinated pyridazines and the two possible trifluorinated pyridazines. The hydrogen fluoride reaction is an equilibrium reaction in which the substitution of the first chlorine for fluorine also occurs exclusively in the 3-position. Double chlorine/fluorine substitution only gives 3,6-difluoro-4,5-dichloropyridazine, triple substitution only producing 3,4,6-trifluoro-5-chloropyridazine.

INTRODUCTION

Fluorine-containing, six-membered nitrogen heterocyclics arouse interest because of their chemical and physical properties [1]. One of these heterocyclics is tetrafluoropyridazine [2, 3, 4], whose synthesis can be effected from tetrachloropyridazine by chlorine/fluorine exchange reactions with potassium fluoride with yields of up to 65 % [3, 4]. We also examined selective chlorine/fluorine exchange reactions on the tetrachloropyridazine system as a function of the various fluorinating agents (NaF, KF and HF) in conjunction with our work on the selective fluorinations of heterocyclics [5, 6].

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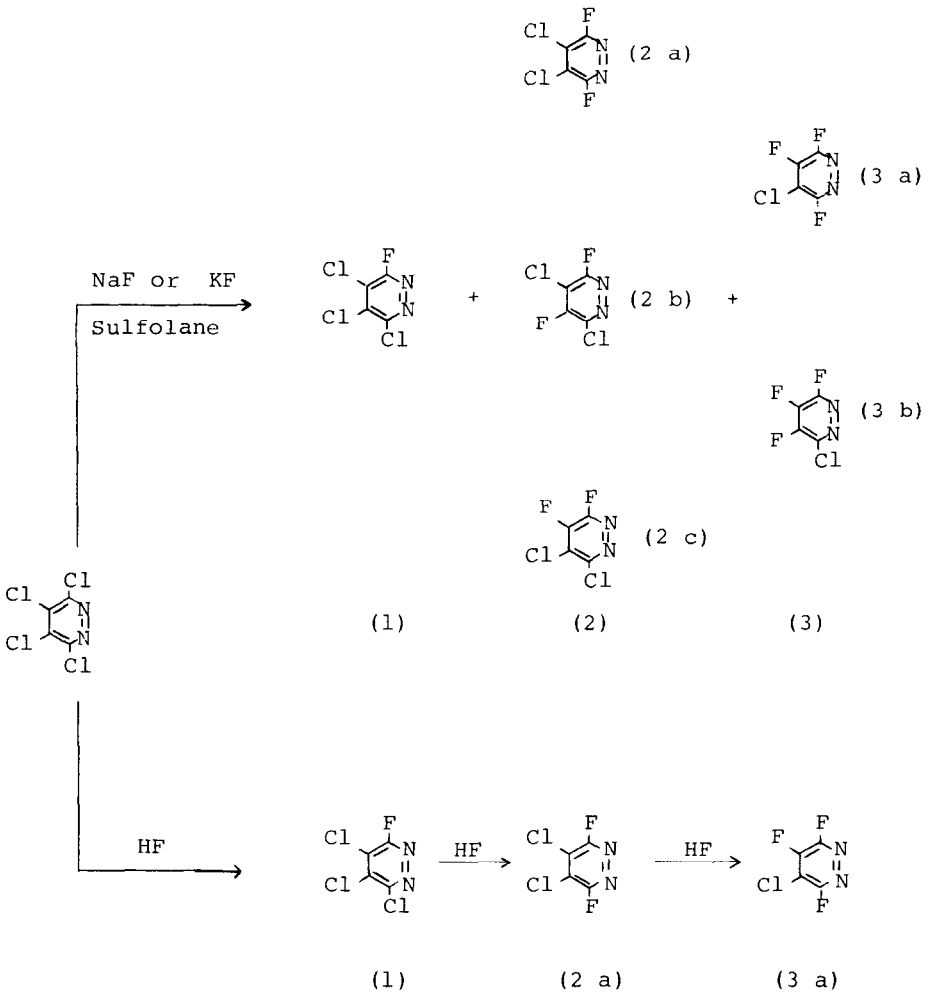
RESULTS AND DISCUSSION

Selective fluorination reactions on tetrachloropyridazine using sodium fluoride and potassium fluoride produce mixtures of the various fluorinating stages (1), (2) and (3) in each case, it being possible to separate the compounds from each other using distillation. The fluorination stage (2) is composed of the difluorinated isomers (2a), (2b) and (2c) while stage (3) is composed of the trifluorinated isomers (3a) and (3b). In contrast to this, the chlorine/fluorine exchange using hydrogen fluoride proceeds selectively as this reaction only yields one isomer for each fluorination stage.



Fluorinations with sodium fluoride and potassium fluoride

It is of no significance whether sodium fluoride or potassium fluoride is used as the fluorinating agent; exchange of the first chlorine atom for a fluorine atom occurs at position 3 on the pyridazine ring so that 3-fluoro-4,5,6-trichloropyridazine (1) is obtained as the only monofluorinated product. The orientation of this exclusive attack at the 3 position is suprising as examinations on tetrafluoropyridazine [3, 4, 7] have shown that the positions 4 and 5 which are para to the nitrogen are, as expected, more strongly activated than positions 3 and 6 in this system and, consequently, are more likely to undergo nucleophilic attack.These orientation rules are also valid when tetrachloropyridazine is reacted with nucleophiles such as ammonia [7] or sodium methanolate [8].

Assuming however that the fluoride anion which is strongly nucleophilic in the aprotic solvent attacks, in a charge-controlled reaction, the position of lowest electron density, that is the 3-position of tetrachloropyridazine, the observed orientation is feasible.

The difluorinated compound fraction (2) consists of a mixture of the three possible isomeric difluorodichloropyridazines, 3,6-difluoro-4,5-dichloropyridazine (2a), 3,5-difluoro-4,6-dichloropyridazine (2b) and 3,4-difluoro-5,6-dichloropyridazine (2c), whose proportions depend on the fluorinating agent. Consequently, the proportion of (2a) arising from the reaction with sodium fluoride is significantly higher at 85 % than in the reaction with potassium fluoride:

Compound		(2 a)	(2 b)	(2 c)
Proportion of the isomer with	NaF	85	11	4
	KF	43	43	14

The trifluorinated pyridazine (3) fraction consists of a mixture of the two possible trifluorinated pyridazines, 3,4,6-difluoro-5-chloropyridazine (3a) and 3,4,5-trifluoro-6-chloropyridazine (3b). The proportion of (3a) is approximately 90 % and does not depend on the fluorinating agent, sodium fluoride or potassium fluoride, with the proportion of (3b) lying at approximately 10 %.

The values quoted for the difluorinated and trifluorinated pyridazine isomer compositions are average values obtained from several reactions carried out under standardized conditions. These conditions are given in Table 1 of the experimental section. The individual isomers (2a), (2b), and (2c) as well as (3a) and (3b) were not separated further preparatively, their determinations and assignments being carried out using gas chromatography, mass spectrometry and, in particular, ^{19}F NMR spectroscopy (Table 3).

Fluorinations with hydrogen fluoride

The chlorine/fluorine exchange reactions with anhydrous hydrofluoric acid are carried out on tetrachloropyridazine under pressure in a closed system at an elevated temperature without the addition of a further fluorination catalyst.

The selective monofluorination using hydrogen fluoride also only yields 3-fluoro-4,5,6-trichloropyridazine (1) after distillation to separate this compound from the starting material still present and from small quantities of the difluorinated product. The reaction conditions can be taken from Table 2 of the experimental section.

If the reaction is carried out with a large excess of hydrogen fluoride (Table 2), 3,6-difluoro-4,5-dichloropyridazine (2a) is obtained as the only difluorinated product. In order to avoid higher degrees of fluorination, this reaction is carried out in such a way that only a conversion of between 30 and 40 % occurs. Correspondingly, triple substitution yields compound (3a) as the only trifluorinated derivative.

These hydrogen fluoride reactions on the pyridazine system are equilibrium reactions, such as we also described them for chlorine/fluorine exchange reactions on pyrimidines [6]. Initially, a ring nitrogen is protonated with subsequent attack of a fluoride anion, conceivably in the 3 or 4 position. It has already been shown [4, 9] for a perfluorinated pyridazine system that an acid-catalyzed nucleophilic substitution occurs exclusively at the 3 position with substitution occuring at the 3 and 6 positions in the case of double attack. An analogous mechanism is obviously also valid for the chlorine/fluorine exchange reactions on tetrachloropyridazine using anhydrous hydrogen fluoride which acts as a reaction medium, a fluoride ion donor and an electrophilic catalyst.

EXPERIMENTAL

Reactions with alkali fluorides

Tetrachloropyridazine, sulfolane and the alkali fluoride are heated with stirring to the reaction temperature. After the relevant reaction period, the mixture is cooled and filtered and the filtrate is fractionally distilled. The experimental and physical data are compiled in Tables 1 and 3. By varying the temperatures and the molar and concentration ratios, the proportions and compositions of the individual fluorination stages can be changed.

TABLE 1

Fluorinations of tetrachloropyridazine (1 molar preparations) with NaF and KF

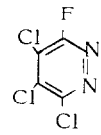
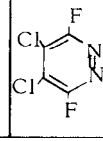
MF	Quantity [g]	Sulfolane [ml]	Temp. [°C]	Time [h]	Product yields (%)		
					(1)	(2a-c)	(3a,b)
NaF	126	375	220	5	36	39	8
KF	174	435	160	5	11	43	19

Reactions with hydrogen fluoride

The anhydrous hydrofluoric acid is placed in a stainless steel autoclave equipped with stirrer, brine-cooled reflux condenser and pressure relaxation valve and the tetrachloropyridazine is added between -5 °C and +5 °C. After completing the addition, the apparatus is sealed, a nitrogen pressure of 10 bar is introduced and the apparatus is heated to the reaction temperature in approximately one hour. The resulting hydrogen chloride is constantly released. Cessation of hydrogen chloride liberation is followed by an aqueous working up with subsequent fractionation or direct distillation. The experimental and physical data are contained in Tables 2 and 3.

TABLE 2

Fluorinations of tetrachloropyridazine
(1 molar preparations) with hydrogen fluoride

HF (mol)	Temp. [°C]	Pressure [bar]	Time [h]	Conversion (%)	Selectivity (%)	Product
10	155	27	2	83	85	 (1)
20	155	27	3	36	67	 (2a)

In the reactions with alkali fluorides and hydrogen fluoride, conversions and yields were not optimized in all cases.

The compounds described were characterized by mass spectroscopy and ^{19}F NMR spectroscopy. The isomer ratios in the mixtures were determined by gas chromatography, the isomer assignments being effected using ^{19}F NMR spectroscopy. The ^{19}F NMR measurements were made on a Bruker WP 80 FT NMR spectrometer with a ^{1}H, ^{19}F dual probe at a measurement frequency of 75.39 Mc/s. The quoted shift values refer to trifluoroacetic acid (δ_{CF_3COOH} = 0 ppm) as the external standard, all spectra being obtained using a $CDCl_3$ solvent. The fluorine atoms neighbouring a nitrogen atom show broadenings due to quadrupole coupling.

TABLE 3

Physical data of pyridazines

Compounds	Substitution				b.p./m.p. [°C]	^{19}F NMR [a], δ (ppm)
	3-	4-	5-	6-		
(1)	F	Cl	Cl	Cl	b.p.:226/m.p. 51	2.13, s (broadened)
(2a)	F	Cl	Cl	F	b.p.: 190/m.p. 48-9	1.98, s
(2b)	F	Cl	F	Cl		1.82, d (3-F); 47.62, d (5-F); J = 25 Hz
(2c)	F	F	Cl	Cl		1.86, d (3-F); 27.59, d (4-F); J = 20 Hz
(3a)	F	F	Cl	F	b.p.: 155 n_D^{20}: 1.4562	0.80, d, d (3-F); 16.58, d, d (6-F), 45.36, d, d (4-F) $J_{3,4}$ = 18 Hz; $J_{4,6}$ = 25 Hz; $J_{3,6}$ = 31 Hz
(3b)	F	F	F	Cl		14.59, t (3-F); 49.08, d, d (5-F); 71.65 d,d (4-F) $J_{3,4}$ = 25 Hz; $J_{4,5}$ = 18 Hz

a) The ^{19}F NMR data for (2b) and (2c) were determined from a mixture with (2a), the data for (3b) being determined from a mixture with (3a).

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