

THE PREPARATION OF N,N-DIFLUOROALKYLAMINES BY AQUEOUS FLUORINATION

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(Received in USA 26 August 1969; Received in the UK for publication 10 October 1969)

Abstract—The aqueous fluorination of N-alkylsulfamides, N-alkylsulfamates and N-alkylsulforamides produced N,N-difluoroalkylamines in good yield. The following compounds were prepared: N,N-difluoromethylamine, N,N-difluoroethylamine, N,N-difluoropropylamine, N,N-difluoroisopropylamine, N,N-difluoro-n-butylamine, N,N-difluoro-sec-butylamine, N,N-difluoroisobutylamine and N,N-difluoro-n-pentylamine. The scope of the reaction is also discussed.

THE interest in N,N-difluoroalkylamines is reflected in the development of numerous syntheses reported during the sixties. These methods generally follow one of two principles. Either the NF₂ group is introduced into the hydrocarbon substrate by reaction with tetrafluorohydrazine or difluoroamine, or a nitrogen-containing compound is fluorinated. Several types of conditions for the fluorination have been employed such as elemental fluorine, interhalogen fluorides or electrochemical fluorination. The use of tetrafluorohydrazine was first accomplished with alkyl iodides employing a unactivated gas phase reaction.² Subsequent investigators utilized azo compounds³ and olefins as the substrate with tetrafluorohydrazine.⁴⁻⁸ Difluoroamine⁹ was found to be a very useful reagent for the amination of carbonium ions.

The application of elemental fluorine in the preparation of N-F compounds was greatly enhanced by the introduction of the aqueous fluorination technique. The use of an aqueous solution of the substrate was initially demonstrated in the preparation of N, N-difluorourea¹⁰ and N,N-difluorosulfamide.¹¹ It soon became apparent that this method could be extended to other substrates. Thus, the fluorination of aqueous solutions of cyanamide,¹² bicarbonate buffered amines¹³ or alkyl substituted ureas¹⁴ produced nitrogen fluorine compounds. The use of elemental fluorine instead of tetrafluorohydrazine or difluoroamine in the preparation of alkyl difluoroamines has the obvious advantages of availability and ease of handling.

RESULTS AND DISCUSSION

N,N-Difluorosulfamide, prepared by the aqueous fluorination of sulfamide, decomposes at temperatures above 5°. Attempts to stabilize the fluorination product by substitution of alkyl groups revealed that cleavage of the N-S bond occurred on fluorination and the corresponding N,N-difluoroalkylamine was formed instead.



In this manner, N,N-difluoroalkylamines containing up to five carbon atoms could

be produced in good yield from the corresponding alkyl sulfamide. No fluorination of the hydrocarbon moiety was observed.

The reaction was not limited to the sulfamide. Rather, *N*-substituted alkylsulfamates and sulfonamides proved equally suitable as substrates



In particular, alkylsulfamates were very useful since they are readily soluble in water and are easily accessible through known syntheses. Water-insoluble substrates could be fluorinated in trifluoroethanol. However, the lower b.p. of the solvent, (74°) began to interfere when less volatile fluoramines were to be produced, and the selectivity of the fluorination suffered.

The reaction was best carried out by passing fluorine, diluted with 70–90% with an inert gas such as nitrogen, helium or argon, into a stirred aqueous solution of the substrate and collecting the volatile products in an external fractionation train. Side reactions could be minimized by performing the fluorination under conditions which reduced the local fluorine concentration and promoted the rapid removal of the product from the reactor. For this reason, better results were obtained with the higher boiling fluoramines when the fluorination was carried out at 20–30° instead of 0° and under partial vacuum. It proved advantageous to introduce the diluted fluorine through a dispersion tube and to provide an additional gas sweep.

The *N,N*-difluoroalkylamines were prepared in yields ranging from 40 to 90% based on the *N* substrate (Table 1). Fluorine utilization was 50–80%. The yields decreased with increasing boiling point. The limiting factor for the scope of the reaction was essentially the volatility of the *N*-F compound. Attempts to extend the applicability to higher boiling products by providing an organic extraction phase during the fluorination were not successful with the unbuffered system.

The exact nature of the active species in the fluorination process is not known. However, the unexpected selectivity of the reaction suggests that it may be highly electrophilic in nature. This is also born out by the selective fluorination of carbonions in aqueous solution^{15–17} and the dependence of the fluorination upon the pH of the solution. Basic substrates such as amines cannot be fluorinated in acidic solutions since the substrate would presumably be protonated and no longer nucleophilic. For example, ammonium salts are completely inert toward aqueous fluorination. A high buffer concentration is therefore necessary to achieve at least moderate yields with amines. The pH of unbuffered amine solutions changes during fluorination from approximately 12 to 3. However, fluoramines are produced only for a short time while the pH is between 8 and 5. While buffering alleviates some of the above mentioned problems it is detrimental to efficient fluorine utilization. Yields based on fluorine are rarely greater than 25% in buffered systems. An effective method to eliminate the need for a buffer is to reduce the basicity of the compound to be fluorinated by substitution. In the case of amines, conversion to the corresponding sulfamide, sulfamate, or sulfonamide proved sufficient. The basicity of the amine nitrogen is thereby reduced to such an extent that protonation becomes negligible. Yet, enough reactivity is retained to bring about fluorination. At pH values above 10, a competitive reaction of the hydroxide ion with the electrophilic fluorinating species produces oxygen difluoride.



Also, any N-F species, if formed at all, would be hydrolyzed. In contrast to N-Cl compounds, fluoramines decompose rapidly in basic solution.

Among the many possible amine derivatives which meet the specified requirements, the sulfone type apparently gives the cleanest reaction. The carbon analogs such as N-substituted areas and carbamates tend to interfere by producing volatile decomposition products from the remaining portion of the substrate. Also, fluorination of the hydrocarbon chain occurs more readily.

The fluorination of sulfamides and sulfamates is not necessarily restricted to the monosubstituted derivative. N,N-dimethylsulfamide was shown earlier to produce dimethylfluoramine upon aqueous fluorination.¹⁸ It is mainly the low volatility and instability of secondary fluoramines which limit the applicability of this fluorination technique to N,N-dialkyl substrates. Symmetrical dialkylsulfamides yield also N,N-difluoroamines but only one of the two amine groups is being utilized in the fluorination.



Apparently, hydrolysis interferes. After the initial fluorination, the remaining fluoro-sulfonamide hydrolyzes rapidly to give the alkylammonium fluorosulfonate or sulfate.

EXPERIMENTAL

Materials. The N-alkylsulfamate salts were prepared by reacting the amine with chlorosulfonic acid.

Preparation of RNF₂ compounds. The compounds prepared are listed in Table 1. The same general procedure was employed throughout. Water was used as the solvent for the N-alkylsulfamate salts and trifluoroethanol for the N-alkyl-*p*-toluenesulfonamides. A five foot piece of rubber vacuum tubing served

TABLE I. FLUORINATION OF N-ALKYL SODIUMSULFAMATES

Product	B.p. °C	Yield %	Temp/Press °C/mm	Calc'd, %			Found, %		
				C	H	N	C	H	N
CH ₃ NF ₂	-16	87	15/760	17.9	4.48	20.9	17.3	4.51	20.1
C ₂ H ₅ NF ₂	15	72	35/760	29.6	6.17	17.3	29.3	6.24	17.4
n-C ₃ H ₇ NF ₂	66-67	67	25/275				37.6	7.31	14.4
iso-C ₃ H ₇ NF ₂	44-45	41	25/275	37.9	7.37	14.7	37.9	7.42	14.9
n-C ₄ H ₉ NF ₂	81-84	71	25/275				43.6	8.12	12.7
iso-C ₄ H ₉ NF ₂	60-62	48	25/275	44.0	8.31	12.8	43.8	8.01	12.4
sec-C ₄ H ₉ NF ₂	86-87	62	25/275				44.2	7.99	13.02
n-C ₅ H ₁₁ NF ₂	102-103	59	25/275	48.8	8.94	11.4	48.2	8.75	11.4

satisfactorily as scrubber to prevent any unreacted fluoroine from entering the pumping system. The preparation of the N,N-difluoromethylamine is given as a typical example:

Into a stirred soln of 0.2 mole (26.8 g) sodium N-methylsulfamate in 400 ml water a stream of fluorine, diluted with 90 vol % helium, was passed at a rate of 2 liters F₂/hr. A gas dispersion tube reaching to the bottom of the flask was used as the gas inlet. The temp of the solution was maintained at 15° by external cooling. The off-gas was passed through a drierite tower into two cold traps (-126°). After 4 hr the fluorine

flow was discontinued and the collected material fractionated through traps maintained at -78 , -126 and -196° , respectively. The product accumulated in the -126° trap and was further purified by low temperature distillation.

A partial vacuum (275 mm) was employed in the fluorination of substrates where the product boiled above 40° . This facilitated the removal of the corresponding N,N-difluoramine from the reactor.

Fluorinations with trifluoroethanol required a 0° reflux condenser at the reactor outlet to avoid loss of solvent.

TABLE 2. FLUORINATION OF N-ALKYL *p*-TOLUENESULFONAMIDES IN TRIFLUOROETHANOL

Product	B.P. °C	Yield %	Temp/Press °C/mm
CH_3NF_2	-16	77	15/760
$n\text{-C}_3\text{H}_7\text{NF}_2$	65-67	82	25/275
$\text{iso-C}_3\text{H}_7\text{NF}_2$	44-46	73	25/275
$n\text{-C}_4\text{H}_9\text{NF}_2$	81-83	70	30/275
$n\text{-C}_5\text{H}_{11}\text{NF}_2$	102-104	50	30/275

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