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PARAMETERS AFFECTING THE PREPARATION OF 3-FLUOROSALICYLALDEHYDE--ETC(U)
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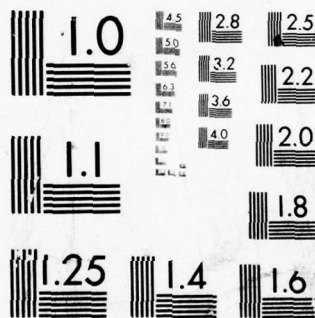
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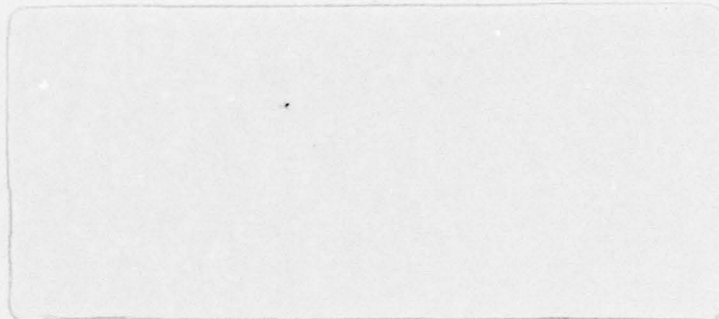
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Final Technical Report
Parameters Affecting the Preparation of
3-Fluorosalicylaldehyde via the
Reimer-Tiemann Reaction

P. A. Pinke and M. D. Tufano
Contract No. F49620-77-C-0104

November, 1977

To

United States Air Force
Air Force Office of Scientific Research
Bolling Air Force Base, D. C. 20337

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| 20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The use of the Reimer-Tiemann reaction for the manufacture of 3-fluorosalicylaldehyde (3-FSA) from ortho-fluorophenol (o-FP) has been looked at in greater detail. Substantial improvements have been made in both the yield of 3-FSA and in the recovery of unreacted o-FP. These improvements have resulted in a manufacturing cost estimate for 3-FSA of \$51-66/lb. The other method developed by UOP, a four-step Claisen route, afforded a manufacturing cost estimate of \$58/lb. These are both improvements over the current manufacturing cost of \$81-400/lb. | | | |

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FOREWORD

This final report was submitted by UOP Corporate Research Center, UOP Inc., Ten UOP Plaza, Des Plaines, Illinois 60016, under Contract No. F49620-77-C-0104 (Parameters Affecting the Preparation of 3-fluorosalicylaldehyde via the Reimer-Tiemann Reaction) with the U.S. Air Force, Air Force Office of Scientific Research, Bolling Air Force Base, D.C. 20332.

The report describes the program conducted by UOP Inc. during the 5-month period from May 1, 1977, to September 30, 1977, and contains the results of laboratory development of improved processes for preparing 3-fluorosalicylaldehyde via the Reimer-Tiemann Reaction. The report was submitted on December 7, 1977.

The work at UOP Inc. was under the supervision of Dr. Paul Pinke Research Chemist. Mr. Michael D. Tufano, Chemist, aided Dr. Pinke in this development work.


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SECTION I

OBJECTIVE AND SCOPE OF WORK

The objective of the work reported herein was to study the parameters affecting the Reimer-Tiemann reaction of ortho-fluorophenol (o-FP) whereby 3-fluorosalicylaldehyde (3-FSA) is made. An improvement in the yield of 3-FSA by the Reimer-Tiemann method would make it a more practical manufacturing procedure. Reducing the cost of 3-FSA manufacture will lower the cost of a cobalt chelate utilizing 3-FSA called fluomine, which is useful for concentrating oxygen from our atmosphere. A fluomine-based breathing system is being developed by the U.S. Air Force for use in aircraft (1).

This work was funded over a five-month period by the United States Air Force, Office of Scientific Research, Bolling Air Force Base, D.C.

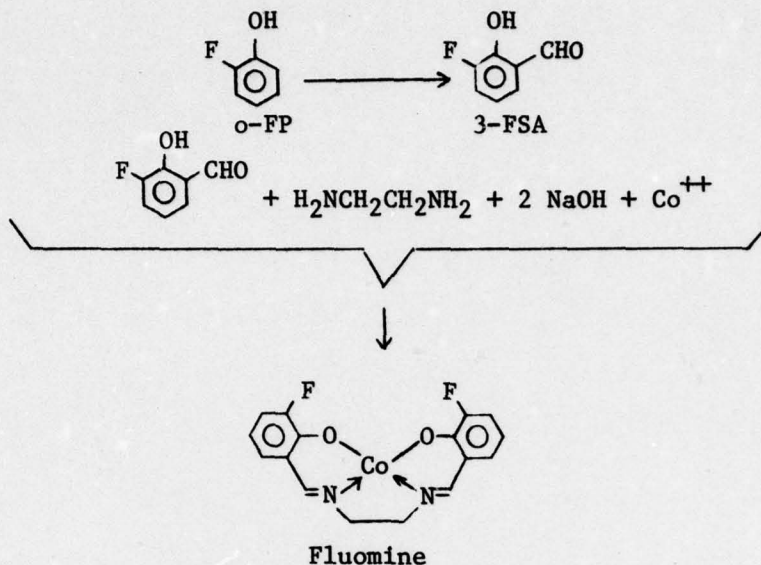
SECTION II

BACKGROUND AND RESEARCH DESIGN

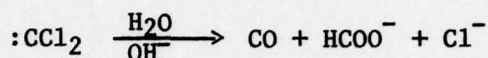
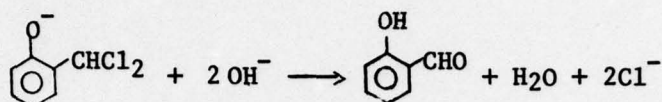
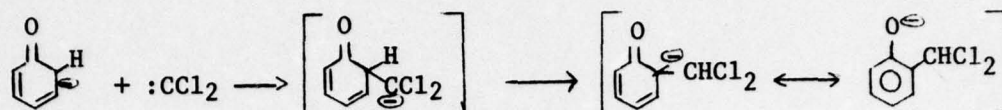
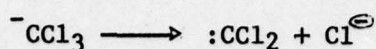
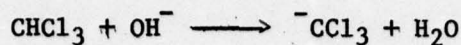
During the 1940's Melvin Calvin and co-workers (2) at the University of California, Berkely, investigated a host of chemicals as potential reversible oxygen sorption materials. Among the more attractive findings was salcomine, a cobalt chelate derived from salicylaldehyde, ethylene diamine and cobalt salts. The 3-fluoro derivative of salicylaldehyde, 3-FSA, afforded a cobalt Chelate called fluomine which was found to be more efficient after many cycles of oxygen adsorption and desorption (2).

Fluomine is being used to develop an oxygen generating system for military aircraft. However, at present, the high cost of fluomine, \$104 (3) to \$500/lb (4) makes the system uneconomical in comparison to more conventional oxygen supply systems. This high cost is due mainly to the cost of 3-FSA \$87 (3) to

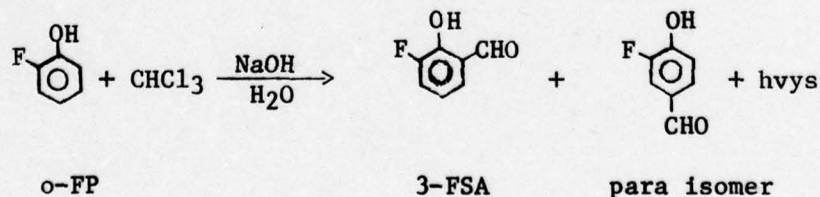
\$400/lb (4) which is a fluomine raw material and the cost of o-FP (\$32 to \$95/lb) which is the 3-FSA raw material.



The Reimer-Tiemann reaction is a general way of preparing hydroxy benzaldehydes by reacting the corresponding phenols with chloroform and aqueous alkali (5). Yields obtained from substituted phenols were usually found to be much lower than from phenol itself. The reaction is believed to involve hydrolysis of chloroform to dichlorocarbene followed by trapping of this short-lived, electron deficient, reactive intermediate by the enolate form of the phenoxide ion (6). One major side reaction, the direct hydrolysis of dichlorocarbene with aqueous alkali to afford carbon monoxide, is not considered significant primarily because its rate is much less than the rate of reaction with phenoxide. However, the presence of an electron withdrawing group (Fluorine) on the aromatic ring would make o-FP a relatively poorer trapping agent than phenol for dichlorocarbene thus increasing the importance of this side reaction.

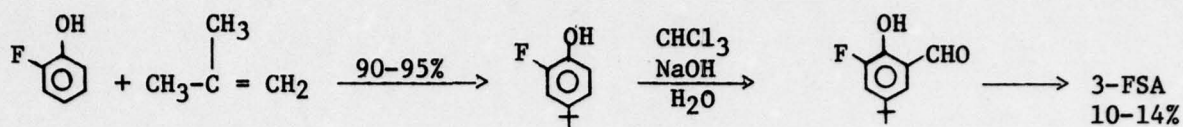


Ferguson, Reich and Calvin (7) reported a 39% conversion of o-FP with a 34% selectivity (13% yield) to 3-FSA and a 39% selectivity to another isomer using a method which consisted of the reaction of CHCl_3 with o-FP and NaOH in an aqueous medium. Attempts to duplicate this work resulted in much lower 3-FSA yields of 0-6% (3) which made this result economically unfeasible. The authors of Report ASD-TR-72-59 attributed this low yield to deactivation of the aromatic ring by the fluorine atom and the availability of only one ortho position which caused formation of substantial quantities of the para isomer (3). Kulka (5) has pointed out that ortho-substituents in general change the Reimer-Tiemann reaction from ortho to para specific.



We have looked at the conversion of o-FP to 3-FSA (8) using water as the reaction medium and have found that the maximum yield from the Calvin procedure was only 10-13%. The use of a tert-butyl group in the position para to the

hydroxyl group of o-FP did not substantially increase the yield of the 3-FSA precursor.



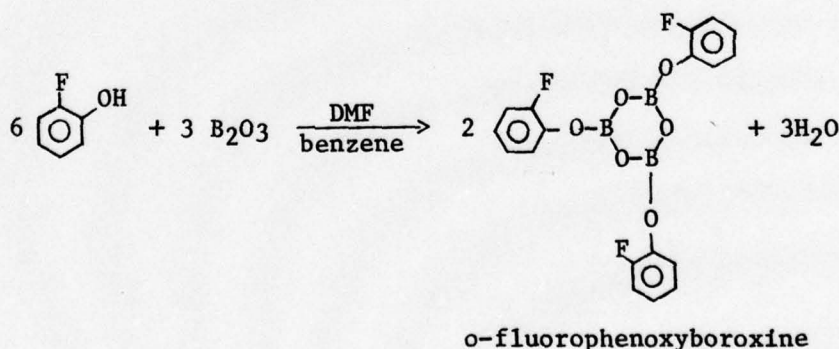
The yield of formulated material improved slightly, however, the improvement in yield was not enough to make this approach any more attractive than the direct formylation of o-FP since it would require three steps.

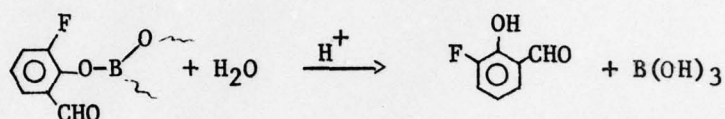
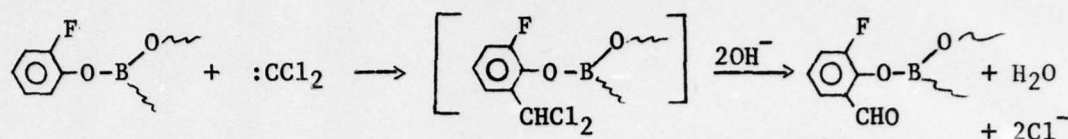
The use of a non-aqueous solvent base, on the other hand, has led to a substantial improvement in the conversion of o-FP which has increased the reproducible yield of 3-FSA to ca. 20%. Selectivities of 26-30% for 3-FSA have been obtained from the use of a solvent system consisting of benzene (6 pts) and t-butanol (1 pt) from the reaction of CHCl_3 with o-FP in the presence of an excess of NaOH. The conversion of o-FP at ca. 65% affords a yield of ca. 20%. This low o-FP conversion creates problems during the reaction work-up and also necessitates a recycle of unreacted o-FP. Attempts to improve the o-FP conversion level resulted in lower yields of 3-FSA. The replacement of water with the benzene/t-butanol solvent system has resulted in a 3-FSA yield increase of over 50%. This improvement in yield and the simplicity of the one-step Reimer-Tiemann reaction has generated new interest in this approach as an effective method for making 3-FSA on a commercial scale.

Two process routes have been developed for the manufacture of 3-FSA from results of our earlier study (8). The most economical of the two processes, the Claisen route, afforded an overall 3-FSA yield of 58% with an estimated manufacturing cost of ca. \$60/lb. This route, however, is complex requiring four steps and would require much development work to reach this level of manufacturing economics. The other process, the Reimer-Tiemann route, afforded

an overall 3-FSA yield of ca. 20% which, when not including any o-FP value for recycle, gave an estimated manufacturing cost of ca. \$140/lb. Even though this route is not as economical, it is still appealing from the standpoint that it is a simple one-step reaction and should require less development work to reach this level of manufacturing economics. It is felt that to be competitive with the Claisen route, the Reimer-Tiemann route would have to afford yields on the order of at least 40%. Therefore, it would be desirable to increase the 3-FSA selectivity obtained from the Reimer-Tiemann reaction.

The use of non-aqueous solvents such as alcohols (9), hydrocarbons plus alcohols or amines (10) and hydrocarbons plus dimethylformamide (11) has been claimed to increase the yields of salicylaldehydes from phenols. With the formation of 3-FSA in mind, workers at AiResearch Manufacturing Co. (11, 12) have reacted o-FP with boron oxide to form a boroxine compound ala Olin Corp. (13). This then is reacted with chloroform and caustic in dimethylformamide (DMF) to give 3-FSA in ca. 10% yield.





Another non-aqueous route involved the use of a sulfone as the solvent for the generation of dichlorocarbene from carbon tetrachloride and caustic (14). In each case, the solvent system which was found the most effective was able to dissolve both ionized and un-ionized materials.

The major variables associated with the Reimer-Tiemann reaction such as reagent ratios, temperature, reaction time, base used, source of dichlorocarbene and work-up procedure were evaluated in terms of improved yield structure. We had previously found that the solvent system had quite an influence on the 3-FSA yield structure and therefore an important part of this effort was directed at the solvent system. This is critical because a substitute for benzene should be found and the effects of the co-solvents and their relative proportions should also be evaluated. Prior to the start of this investigation, it was noted that the status on the use of benzene as a reaction solvent had changed considerably. The reported toxicity of benzene (15) places severe restrictions on its use as a solvent in large-scale reactions. A brief study of the by-products formed during this reaction may afford more information about the overall direction of the Reimer-Tiemann reaction for this fluorinated phenol.

SECTION III

RESEARCH RESULTS AND DISCUSSION

Our previous best results for the Reimer-Tiemann reaction (8) were obtained by the slow addition of CHCl_3 (.356 moles) to a stirred mixture of o-FP (.178 moles) and NaOH (1.01 moles) in a solvent system of benzene (214 ml) and t-butanol (36 ml). Our highest yield to date was a 26% 3-FSA selectivity at a 95% o-FP conversion for a yield of ca. 25%. These results will be referred to during the course of this discussion as improvements are presented. Our investigation of other aromatic compounds similar to benzene looking for a suitable replacement was the point at which this work was begun.

SOLVENT VARIATIONS

A limited number of experiments were carried out with this improved Reimer-Tiemann reaction looking at variations in the aromatic component of the solvent system with the goal of finding an acceptable replacement for benzene. Also during this phase of the study the alcohol component and other materials which were believed to have an effect on the Reimer-Tiemann reaction were investigated. These results are presented in the first half of Table 1. Under the reaction conditions used for evaluating the influence of the aromatic component of the solvent system, it was found that toluene (Expt. Nos. 9, 11 and 15) was at least as good if not better than benzene (Expt. No. 13) or chlorobenzene (Expt. No. 7) with a 3-FSA yield of 17-24% vs. 3-FSA yields of 16% and 15%, respectively. There was concern that toluene, being a more active molecule than benzene, would itself conceivably become involved in the Reimer-Tiemann reaction, however, we have not found any evidence for this in the form of a methyl substituted benzaldehyde. Thus, based on this limited experimentation with simplicity, boiling range, and cost of the aromatic system in mind, it was decided that toluene would be the aromatic solvent of choice.

Table 1

Non-Aqueous Reimer-Tiemann Reactions Covering Effects of Solvent and Work-up^a

| Expt.No. 3585- | ← Solvent → | | | Time, hr ^b | | Temp, °C | CHCl ₃ ^c | o-FP ^d | 3-FSA ^e | 3-FSA ^f | Comments |
|---------------------------------|---------------|---------|--------------------|-----------------------|---------|----------|--------------------------------|-------------------|--------------------|--------------------|--------------------------------|
| | Aromatic | Alcohol | Other ^g | A / T | Conv, % | | Conv, % | Sel, % | Yield, % | | |
| Solvent Variations | | | | | | | | | | | |
| -5 | benzene | t-BUOH | - | 1 | 3 | 65 | 65 | 60 | 26 | 15 | |
| -13 | " | " | - | .6 | 3 | 70 | 70 | 73 | 23 | 16 | |
| -7 | Chlorobenzene | " | - | 1 | 3 | 65 | 72 | 56 | 27 | 15 | |
| -1 | Toluene | " | - | 1.5 | 3 | 65-88 | 76 | 88 | 11 | 10 | |
| -9 | " | " | - | .6 | 3 | 70 | 71 | 64 | 36 | 24 | |
| -11 | " | " | - | .6 | 3 | " | 76 | 58 | 29 | 17 | |
| -15 | " | " | - | .6 | 1.5 | " | 54 | 60 | 36 | 22 | |
| -27 | " | IPA | - | .6 | .6 | " | 61 | 56 | 34 | 19 | |
| -31 | " | t-buOH | Ratio 1:1 | .6 | .6 | " | 62 | 73 | 24 | 17 | |
| -59 | " | DMF | Ratio 6:1 | .6 | 1.5 | " | 52 | 30 | 21 | 6 | |
| -67 | " | ETOH | Ratio 6:1 | .6 | 1.5 | " | 75 | 63 | 21 | 13 | |
| -39 | " | t-buOH | PT Cat | .6 | 1.5 | " | 75 | 63 | 21 | 13 | |
| -63 | " | " | PT Cat | .6 | 1.5 | " | - | 54 | 14 | 8 | |
| -71 | " | " | Tetraglyme | .6 | 1.5 | " | 73 | 84 | 7 | 6 | |
| Work-up Variations ^h | | | | | | | | | | | |
| -15 | Toluene | t-buOH | - | .6 | 1.5 | 70 | 54 | 60 | 36 | 22 | base/acid |
| -35 | " | " | - | .6 | 1.5 | 70 | 63 | 65 | 43 | 28 | acid |
| -43 | " | " | - | .6 | .6 | 80 | - | 66 | 31 | 20 | Non-Dist. |
| -17 | " | " | - | .6 | .6 | 70 | 72 | 42 | 35 | 15 | Rapid Q. |
| -51 | " | " | - | .6 | .6 | 80 | 75 | 67 | 45 | 30 | PT Cat |
| -19 | " | " | - | .6 | 1.5 | 70 | 58 | 59 | 30 | 17 | H ₃ PO ₄ |

^aThe normal procedure involved the addition of CHCl₃ (.356 moles) to the suspension containing o-FP (.178 moles), NaOH (1.01 moles) in the appropriate solvent which had a total volume of 250 ml usually in a 6:1 ratio of aromatic to alcohol.

^bThe two times reported are the time of CHCl₃ addition (A) and the total reaction time (T).

^cThe conversion of CHCl₃ was based on the amount of material remaining at the end of the reaction time as determined by GC.

Table 1 (Cont'd)

^dThe o-FP conversion was determined as the material lost during the reaction based on GC analysis.

^eThe 3-FSA selectivity is based on moles of product divided by moles of o-FP converted.

^fThe yield of 3-FSA is the result of the multiplication of conversion and selectivity and is of value only if the unreacted o-FP cannot be recycled.

^gUnder the other category is reported a different ratio for aromatic and alcohol, a Phase Transfer Catalyst-benzyltrimethyl ammonium chloride, and tetraglyme-tetraethyleneglycol dimethyl ether a system similar to the crown ethers but far more economical.

^hWork-up variations dealt with how the reaction mixture was treated in order to recover the 3-FSA and o-FP. These are discussed in the results section.

Replacement of the t-butanol component of the reaction system with either ethanol (Expt. No. 67), isopropanol (Expt. No. 27) or dimethylformamide (Expt. No. 59) was not encouraging with 3-FSA yields of 13%, 19%, and 6% respectively vs. 17-24% for t-butanol. It is possible that the isopropanol could be developed as a replacement for t-butanol if the economics warranted, however, the cost of recoverable solvent was small relative to the cost of the o-FP. A variation in the ratio of aromatic to alcohol (Expt. No. 31 at a ratio of 1:1 vs. Expt. No. 15 at a ratio of 6:1) suggests that the reaction is not grossly affected by changes in this ratio with 3-FSA yields of 17% and 22% respectively. There is, however, a better 3-FSA yield from the 6:1 ratio of toluene to t-butanol.

The addition of another component to the toluene-t-butanol based system such as a phase transfer agent or a material similar in properties to a crown ether-tetraglyme was found to have a deleterious effect on the 3-FSA yield. The use of the oxygen complexing agent-tetraethylenglycol dimethyl ether (Expt. No. 71) increased the conversion of o-FP but drastically reduced the 3-FSA yield to 6%. Thus, it is evident that these additives do not have a positive effect on the Reimer-Tiemann reaction run under these conditions.

Work-up Variations

During the early part of this work it was found that variations in the work-up procedure afforded different yields of the desired 3-FSA. The work-up procedure used to this point involved the addition of water to the reaction mass followed by distillation to remove the organics. The distillation residue was then acidified with HCl to free the phenolics followed by steam distillation of the o-FP/3-FSA mixture. Steam distillation of the o-FP/3-FSA mixture required a large amount of water (ca. 500 ml per 20g o-FP charged). This large amount of water made it difficult to separate and recover the majority of the water soluble o-FP and 3-FSA. Solvent extraction could only recover a limited percentage of the total. The use of a Dean-Stark trap which recycled the water layer from the condensed distillate allowed the concentration of o-FP and 3-FSA. This concentration afforded a more accurate accounting of the reagents. This explains why conversion levels of o-FP are not as high as 90-100% as previously reported. This improved work-up procedure recovered more o-FP than the original method.

The results of experiments involving variations in the work-up procedure are presented in the lower half of Table 1. The standard procedure which involved distillation afforded a 3-FSA yield of 22% (Expt. No. 15). If, on the other hand the reaction mass is acidified prior to its first distillation (Expt. No. 35) and the solvents are separated from the o-FP/3-FSA mixture, then the yield of 3-FSA is increased to 28% at about the same level of o-FP conversion. Use of an extractive procedure (Expt. No. 43) which would not involve distillation afforded a 3-FSA yield of only 20% at about the same o-FP conversion level. The extractive procedure involved several toluene washes until only trace amounts of o-FP and 3-FSA could be removed per wash. This demonstrates that either one needs the added heat to obtain the optimum yield of 3-FSA or that there is again

too much solvent. The elevated temperature of this run (80°C vs. usual 65-70°C) can be discounted and will be discussed later. The use of a rapid acid quench (Expt. No. 17), which neutralized the mixture after addition was complete, demonstrates that under these conditions the Reimer-Tiemann reaction is not rapid enough to convert the CHCl_3 as quickly as it is added to the reaction. A 3-FSA yield of only 15% was obtained from an o-FP conversion of only 42% versus the normal 60-65% o-FP conversion level. The addition of a phase transfer catalyst to the reaction mass just prior to acid hydrolysis (Expt. No. 51) appears to improve the yield of 3-FSA to 30% at an o-FP conversion of 67%, however, the elevated temperature of this run (80°C) which will be discussed later will demonstrate that the phase transfer agent probably had little or no effect on the 3-FSA yield. Finally, the use of another, less corrosive acid to hydrolyze the reaction mass- H_3PO_4 - (Expt. No. 19) was found to afford a lower 3-FSA yield of 17% at about the same level of o-FP conversion. Thus, it is clear that the 3-FSA yield can be improved by acidification of the reaction mass with HCl prior to distillation of any of the components. This is understandable since, after the base/acid workup the sodium phenoxide was heated to 100-110° under a strongly caustic surrounding and one might expect more side product formation by this method. This approach was followed throughout most of the remaining investigation.

Base Variables

During the previous investigation (8) the majority of the work carried out on the non-aqueous system used NaOH as the source of base. An early portion of this investigation was directed towards other possible base systems. The results obtained from looking at these base systems are presented in Table 2. Under the conditions chosen for this study, a reaction temperature of 70°C with the earlier used base/acid work-up, we found that NaOMe and NaOH (Expt. Nos. 21 and 15)

Table 2

Non-Aqueous Reimer-Tiemann Reactions Centered Around NaOH as the Base^a

| Expt.No. | Base Used | Time, hr ^b | | Temp, °C | CHCl ₃ ^c | o-FP ^d | 3-FSA ^e | 3-FSA ^f | Comments |
|---|-----------|-----------------------|------|----------|--------------------------------|-------------------|--------------------|--------------------|---|
| 3585- | | A | T | | Conv, % | Conv, % | Sel, % | Yield, % | |
| <u>Base Variables</u> (base/acid work-up) | | | | | | | | | |
| -15 | NaOH | .6 | 1.5 | 70 | 54 | 60 | 36 | 22 | |
| -29 | LOH | .6 | 1.5 | " | ~0 | ~0 | - | - | |
| -45 | KOH | .6 | .6 | " | 65 | 67 | 15 | 10 | |
| -21 | NaOMe | .6 | 1.5 | " | 85 | 69 | 30 | 21 | |
| -65 | NaOt-bu | .6 | 1.5 | " | 88 | 70 | 19 | 14 | |
| <u>Temperature</u> (base/acid work-up) | | | | | | | | | |
| -15 | NaOH | .6 | 1.5 | 70 | 54 | 60 | 36 | 22 | |
| -23 | NaOH | .6 | 1.5 | 80 | 64 | 78 | 37 | 29 | |
| -33 | NaOH | .6 | 1.5 | 85-90 | 42 | 73 | 35 | 26 | |
| <u>Addition Time</u> (acid work-up) | | | | | | | | | |
| -83 | NaOH | .15 | .33 | 80 | 38 | 49 | 33 | 16 | |
| -79 | " | .33 | .33 | " | 26 | 53 | 41 | 22 | |
| -73 | " | .66 | .66 | " | 46 | 62 | 46 | 28 | |
| -77 | " | 1.5 | 2.25 | " | 56 | 75 | 37 | 28 | |
| -49 | " | 2.0 | 2.35 | " | - | 71 | 35 | 25 | Scale-up ^g |
| -25 | " | .6 | .6 | 70 | 64 | 62 | 29 | 18 | Simultaneous Add'n o-FP, CHCl ₃ |
| <u>Reproducibility</u> (acid work-up) | | | | | | | | | |
| -41 | NaOH | .6 | .6 | 80 | 64 | 65 | 46 | 30 | |
| -47 | " | .6 | .6 | " | 50 | 59 | 41 | 24 | See h below |
| -69 | " | .6 | .6 | " | 52 | 65 | 43 | 28 | |
| -73 | " | .6 | .6 | " | 46 | 62 | 46 | 28 | |

^aThe normal procedure involved the addition of CHCl₃ (.356 moles) to the suspension of o-FP (.178 moles) and caustic (1.01 moles) in toluene (214 ml) and t-butanol (36 ml).

^bThe two times reported are the time of CHCl₃ addition (A) and the total reaction time (T).

^cThe conversion of CHCl₃ was based on the amount of material remaining at the end of the reaction time as determined by GC.

^dThe o-FP conversion was determined as the material lost during the reaction based on GC analysis of recovered o-FP.

^eThe 3-FSA selectivity is based on moles of product divided by moles of o-FP converted.

^fThe yield of 3-FSA is the result of the multiplication of conversion and selectivity and is of value only if the unreacted o-FP cannot be recycled.

^gThe scale-up run was run at a factor of 10 times larger than the other work.

^hLower yield could be due to the fact that the acidified reaction contents were exposed to the air over a weekend period and thus possibly suffered from more air oxidation of the 3-FSA.

afforded comparable yields of 3-FSA at 21% and 22% respectively but with the NaOMe causing a higher o-FP conversion, 69% vs. 60%. The other bases evaluated, LiOH, KOH and NaO-t-butyl (Expt. Nos. 29, 45 and 65) afforded 3-FSA yields of 0%, 10% and 14% with o-FP conversions of 0%, 67% and 70%. It appears from these results that NaOMe may be comparable to NaOH as a base or even slightly more active judging from the higher levels of conversion for both the CHCl₃ and o-FP.

Temperature

With benzene as the solvent of choice prior to this study, we were limited in reaction temperature by the boiling point of the benzene-CHCl₃ solution which suggested that 70°C would be an easy temperature to control. With a switch to toluene we have been able to look at more elevated temperatures and have found that 80°C appears to be a much better operating temperature. On comparison of three reaction temperatures, 70°C, 80°C and 85-90°C (Expt. Nos. 15, 23, 33) we found that the o-FP conversion went from 60% to 78% to 73% while the 3-FSA yield went from 22% to 29% to 26%. Therefore, a temperature range of around 80°C would be most optimal.

Addition and Reaction Time

The reaction system which used NaOH as the base was found to require a longer reaction time than just the CHCl₃ addition time. This was found to be the case when run at 80°C, and quenched immediately after a short CHCl₃ addition time, thus the conversions and yields were lower than those obtained after an extended reaction time period was allowed. As the reaction time was increased from 0.33 hr to 2.25 hr (Expt. Nos. 83, 79, 73 and 77) we found that the o-FP conversion continued to increase from 49% to 75% while the 3-FSA yield increased from 16% up to 28%. Thus, this strongly suggests that a longer time spent during the controlled addition of CHCl₃ should not result in a decrease of 3-FSA yield.

However, when this was scaled-up by a factor of 10 (Expt. No. 49) which had a longer addition time of 2.0 hr and a total reaction time of 2.35 hr, there was afforded a slightly lower 3-FSA yield at 25%. As a means of controlling the exothermic nature of the reaction, the simultaneous addition of o-FP and CHCl_3 was attempted (Expt. No. 25) at 70°C. The conversion of o-FP was normal at 62% but the yield of 3-FSA was only 18% a little below the normal result of ca. 22% under these conditions.

Alternate Source of Dichlorocarbene

The use of sodium trichloroacetate as a possible source for dichlorocarbene (Expt. No. 61) in this non-aqueous solvent system was not successful with an o-FP conversion of 59% but no evidence of the formation of any 3-FSA.

Sodium Alkoxide As Base

The results from the use of NaOMe as a replacement base for NaOH in this specific non-aqueous Reimer-Tiemann work (Table 2, Expt. Nos. 21 and 15) were suggestive that the NaOMe might be a more effective base. A look at other similar alkoxide bases (Table 3) demonstrates that when this reaction is carried out at 80°C NaOMe and NaOEt are slightly better in yield effectiveness compared to NaOH. Under comparable conditions NaOMe and NaOEt (Expt. Nos. 75 and 101) afforded o-FP conversions of 56% and 47% with 3-FSA yields of 28% and 26% while NaOH (Expt. No. 73, Table 2) afforded an o-FP conversion of 62% with a 3-FSA yield of 28%. With lower o-FP conversion for the two alkoxides there is more o-FP for recycle. A higher level of CHCl_3 conversion at 75-76% was observed for the alkoxide base versus 46% for NaOH, however, the price of CHCl_3 is not significant in the overall reaction scheme. These results suggest that further work be carried out on other alkoxide systems. The other alkoxide and related base systems evaluated, the sodium salts of isopropanol, t-butanol and NH_3 as well as LiOMe (Expt. Nos. 118, 99, 103 and 76, Table 3) afforded, under comparable

Table 3

Non-Aqueous Reimer-Tiemann Reactions Based On Using Sodium Alkoxide as the Base^a

| Expt.No. 3585- | Base Used | Time, hr ^b A / T | | Temp, °C | Ratio CHCl ₃ :o-FP | CHCl ₃ ^c Conv, % | o-FP ^d Conv, % | 3-FSA ^e Sel, % | 3-FSA ^f Yield, % |
|--|-------------------|--------------------------------|-----|----------|----------------------------------|---|------------------------------|------------------------------|--------------------------------|
| Base | | | | | | | | | |
| -75 | NaOMe | .6 | .6 | 80 | 2 | 76 | 56 | 51 | 28 |
| -101 | NaOEt | .6 | .6 | " | " | 75 | 47 | 56 | 26 |
| -118 | NaOisoP | .6 | .6 | " | " | 87 | 58 | 28 | 16 |
| -99 | NaO-t-bu | .6 | .1 | " | " | <5 | 22 | 41 | 9 |
| -103 | NaNH ₂ | .6 | .6 | " | " | 85 | 42 | 12 | 5 |
| -76 | LiOMe | .6 | .6 | " | " | NR | <10 | - | - |
| CHCl ₃ :o-FP Ratio | | | | | | | | | |
| -87 | NaOMe | .3 | .3 | " | 1 | ~100 | 38 | 67 | 26 |
| -93 | " | .3 | .3 | " | 1.5 | ~100 | 51 | 55 | 28 |
| -91 | " | .3 | .9 | " | 1.5 | ~100 | 53 | 51 | 27 |
| -85 | " | .3 | .3 | " | 2 | 68 | 52 | 55 | 29 |
| -75 | " | .6 | .6 | " | 2 | 76 | 56 | 51 | 28 |
| -81 | " | .6 | .6 | " | 3 | 61 | 52 | 55 | 29 |
| Time and Temp. | | | | | | | | | |
| -75 | NaOMe | .6 | .6 | 80 | 2 | 76 | 56 | 51 | 28 |
| -21 | " | .6 | 1.5 | 70 | " | 85 | 69 | 30 | 21 |
| -89 | " | 1.5 | 2.3 | 80 | " | 71 | 55 | 57 | 31 |
| Alcohol Replacement ^g | | | | | | | | | |
| -97 | NaOMe | .3 | .3 | 80 | 2 | 57 | 13 | 10 | 1 MeOH for t-buOH |
| Level of Base and Concentration ^h | | | | | | | | | |
| -75 | NaOMe | .6 | .6 | 80 | 2 | 76 | 56 | 51 | 28 ^{B: o-FP = 5} |
| -119 | " | .6 | .6 | " | " | 26 | 21 | 42 | 9 ^{B: o-FP = 7.5} |
| -135 | " | .6 | .6 | " | " | 32 | <15 | Low | - Sol- vent ¹ |

^aThe normal procedure involved the addition of CHCl₃ (.356 moles) to the suspension of o-FP (.178 moles) and sodium alkoxide (1.01 moles) in toluene (214 ml) and t-butanol (36 ml).

^bThe two times reported are the time of CHCl₃ addition (A) and the total reaction time (T).

^cThe conversion of CHCl₃ was based on the amount of material remaining at the end of the reaction time as determined by GC.

^dThe o-FP conversion was determined as the material lost during the reaction based on GC analysis of recovered o-FP.

^eThe 3-FSA selectivity is based on moles of product divided by moles of o-FP converted.

^fThe yield of 3-FSA is the result of the multiplication of conversion and selectivity and is of value only if the unreacted o-FP cannot be recycled.

^gMeOH was used as the complete replacement for t-butanol.

^hNormal ratio of base to o-FP was 5.0, increase in this ratio was to 7.5. Also, since the o-FP concentration was low (8-10%) a doubling of concentration to ca. 20% was tried.

conditions, similar or lower levels of o-FP conversion with much lower 3-FSA yields of from 0-16%. Thus, it appears that the sodium salts of MeOH and EtOH would be good bases for the non-aqueous Reimer-Tiemann reaction.

Temperature

Similar to the work using the base NaOH, use of a higher temperature (80°C) and a longer reaction time afforded a better 3-FSA yield. The use of a 70°C reaction temperature and a short (0.6 hr) reaction time (Expt. Nos. 21 and 75) afforded lower 3-FSA yields of 21% and 28% relative to the higher temperature and longer reaction time (Expt. No. 89) which afforded a 3-FSA yield of 31%. It is very interesting to note that with the lower reaction temperature more of the CHCl_3 and o-FP have been converted but that the 3-FSA selectivity is much lower at 30% vs. 51-57% for the 80°C work. One could speculate that the reaction temperature is a very critical factor in this system with the optimum temperature approximately 80°C.

Ratio of CHCl_3 :o-FP

Our previous work (8) discussed the influence of the CHCl_3 :o-FP ratio on the yield of 3-FSA and it was concluded that a ratio of ca. 2.0 was optimum when NaOH was used as the base. The use of NaOMe to replace NaOH prompted us to reinvestigate the effect of this CHCl_3 :o-FP ratio. With an excess of CHCl_3 present there does not appear to be a significant influence of the CHCl_3 :o-FP ratio on either the level of o-FP conversion or 3-FSA yield. The use of a CHCl_3 :o-FP ratio of from 2-3 (Expt. Nos. 85, 75 and 81) afforded o-FP conversions of 52-56% with 3-FSA yields of 28-29% while the amount of CHCl_3 converted ranged from 61-76% of that charged. When the CHCl_3 :o-FP ratio ranged from 1.0-1.5 (Expt. Nos. 87, 93 and 91) the o-FP conversion ranged from 38% for the 1.0 ratio to 51-53% for the 1.5 ratio with respective 3-FSA yields of 26% and 27-28%. The use of a CHCl_3 :o-FP ratio of around 1.0 appears to be the optimum in terms of

3-FSA selectivity, which, at 67% was the highest selectivity observed in this study. It is unfortunate, however, that at this higher selectivity, the level of o-FP conversion is quite low at 38%. But, one must keep in mind that the difference between a low o-FP conversion of 38% and the usually observed 50-60% is quite small in terms of the extra cost of recycle. Since the yield obtained from this low conversion reaction was 26% 3-FSA it is not far away from the maximum 3-FSA yield of 29-31%. Therefore, from these results, the optimum ratio of CHCl_3 :o-FP should be around 1.0.

Solvent

In all this work, the use of t-butanol as a co-solvent in the NaOH based system has been recommended over any of the other alcohols evaluated. When working with NaOMe it is known that its reaction with o-FP would release some MeOH which may help or hinder this reaction. Replacement of the t-butanol with methanol (Expt. No. 97) produced a dramatic decrease in 3-FSA yield. In this case the o-FP conversion dropped to 13% and the 3-FSA yield dropped to 1%. Clearly, some methanol is advantageous because the use of the sodium tert-butoxide in addition to tert-butanol (Expt. No. 99) also afforded a lower o-FP conversion (22%) and a lower 3-FSA yield (9%). The amount of methanol required for optimized 3-FSA yield is not known and further work would be needed to demonstrate this.

Other variables which were briefly examined were the ratio of base:o-FP and the amount of solvent used. When the base:o-FP ratio was increased from 5, the usually run ratio, to 7.5 (Expt. Nos. 75 and 119) the conversion of o-FP decreased from 56% to 21% and the 3-FSA yield decreased from 28 to 9%. When the concentration of reactants was doubled (Expt. No. 135) the mixture was viscous and difficult to stir and the conversion of o-FP was found to be very low at <15% with hardly any 3-FSA formed.

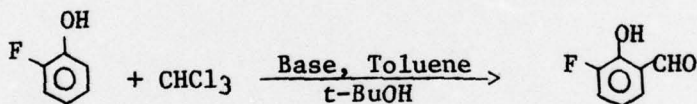
The results obtained from the use of the sodium alkoxides demonstrate an even further improvement in o-FP conversions at ca. 53-56% with 3-FSA yields of 28-31%. With effective recycle of unreacted o-FP we can possibly obtain 3-FSA yields of up to 55-57%.

SECTION IV

MANUFACTURING COST ESTIMATE

The cost estimates presented below are based on yield structures developed during the course of this work. It should be pointed out, however, that all reactions were conducted in laboratory equipment. Therefore, scale-up development will be necessary to provide more accurate cost estimates prior to commercialization. These estimates assume that all unreacted o-FP can be recovered for re-use, therefore, the selectivity values will be used in these calculations instead of the yield values.

Chemistry



| <u>No.</u> | <u>Expt.No.</u> | <u>Conversion</u> | <u>Selectivity</u> | <u>Comments</u> |
|------------|-----------------|-------------------|--------------------|------------------------------------|
| 1 | -69 | 65% | 43% | NaOH |
| 2 | -87 | 38% | 67% | NaOMe, CHCl ₃ :o-FP = 1 |
| 3 | -75 | 56% | 51% | NaOMe, CHCl ₃ :o-FP = 2 |

Table 4

3-FSA Raw Material Costs (Results for System No. 1)

| | <u>Net lbs</u> | <u>Lbs/lb</u> | <u>Std \$/lb</u> | <u>\$/lb 3-FSA</u> |
|------------------|----------------|---------------|------------------|--------------------|
| o-fluorophenol | 932 | 1.86 | 32.0 | 59.52 |
| sodium hydroxide | 2542 | 5.08 | .25 | 1.27 |
| chloroform | 1991 | 3.98 | .20 .26 | .79 |
| t-butyl alcohol | 5 | .01 | .10 | .003 |
| toluene | 10 | .02 | .015 | .002 |
| muratic acid | 7570 | 15.29 | .40 | .23 |
| methanol | 1630 | 3.29 | .075 | 1.32 |
| hexane | 100 | .2 | | .02 |
| | 500 | | | \$63.15 |

Table 5

3-FSA Raw Material Costs (Results for System No. 2)

| | <u>Net lbs</u> | <u>Lbs/lb</u> | <u>Std \$/lb</u> | <u>\$/lb 3-FSA</u> |
|------------------|----------------|---------------|------------------|--------------------|
| o-fluorophenol | 598 | 1.20 | 32.0 | 38.40 |
| sodium methoxide | 1631 | 3.26 | .94 | 3.06 |
| chloroform | 637 | 1.27 | .20 | .25 |
| t-butyl alcohol | 5 | .01 | .26 | .003 |
| toluene | 10 | .02 | .10 | .002 |
| muratic acid | 7570 | 15.14 | .015 | .23 |
| methanol | 1630 | 3.26 | .40 | 1.32 |
| hexane | 100 | .20 | .075 | .02 |
| 3-FSA | 500 | | | \$43.29 |

Table 6

3-FSA Raw Material Costs (Results for System No. 3)

| | <u>Net lbs</u> | <u>Lbs/lb</u> | <u>Std \$/lb</u> | <u>\$/lb 3-FSA</u> |
|------------------|----------------|---------------|------------------|--------------------|
| o-fluorophenol | 785 | 1.57 | 32.0 | 50.24 |
| sodium methoxide | 2143 | 4.28 | .94 | 4.02 |
| chloroform | 838 | 1.67 | .20 | .33 |
| t-butyl alcohol | 5 | .01 | .26 | .003 |
| toluene | 10 | .02 | .10 | .002 |
| muratic acid | 7570 | 15.14 | .015 | .23 |
| methanol | 1630 | 3.26 | .40 | 1.32 |
| hexane | 100 | .20 | .075 | .02 |
| 3-FSA | 500 | | | \$56.17 |

In order to compare results of this study with previously reported results (8) we have followed the same format of cost estimating.

Added value costs for producing 3-FSA this way in small batches (500 lbs) on a non-continuous basis might be ca. 150% of "normal" raw material costs. o-Fluorophenol at \$32/lb is not the usual kind of chemical; therefore, we have estimated added value to be 150% of material costs assuming phenol at 25¢/lb instead of o-FP.

Table 7
3-FSA Manufacturing Cost Estimates

| | \$/lb 3-FSA | | |
|--------------------|-------------|-------------|-------------|
| | <u>#1</u> | <u>#2</u> | <u>#3</u> |
| o-fluorophenol | \$59.52 | \$38.40 | \$50.24 |
| Other Chemicals | 3.63 | 4.89 | 5.93 |
| <u>Added Value</u> | <u>6.14</u> | <u>7.78</u> | <u>9.48</u> |
| Manufacturing Cost | \$69.29 | \$51.07 | \$65.65 |

SECTION V

SUMMARY

The Reimer-Tiemann approach to the manufacture of 3-FSA from o-FP has been more closely examined. This direct, one-step process had been investigated previously by other workers; it involved the reaction of o-FP with chloroform under aqueous alkaline conditions. A 39% o-FP conversion with a 34% selectivity to 3-FSA (based on converted o-FP) had been reported earlier (2), but later workers obtained only 0-6% yields (3). By employing non-aqueous conditions and using an excess of chloroform and caustic we had obtained 95% o-FP conversion with 26% selectivity to 3-FSA (8). A manufacturing cost estimate of \$140/lb was determined based on that yield structure obtained from lab scale results.

Our re-investigation of the non-aqueous reaction along with further development work on the work-up procedure has afforded better results from this approach. Using NaOH and the better procedure we have been able to obtain a 65% o-FP conversion with a 43% 3-FSA selectivity for a much improved manufacturing cost estimate of ca. \$70/lb, 50% of the previous cost estimate. This of course assumes the effective recycle of unreacted o-FP which did not pose a problem in the previous study with 95% o-FP conversion. The use of sodium methoxide as the base afforded better 3-FSA selectivities and a slightly more reactive system.

One reaction carried out with a 1:1 ratio of CHCl_3 to o-FP afforded a 38% conversion of o-FP with a 67% selectivity to 3-FSA. This gave a manufacturing cost estimate of ca. \$51/lb for 3-FSA. The use of an excess of chloroform with a CHCl_3 :o-FP ratio of 2 gave a 56% conversion of o-FP with a 51% 3-FSA selectivity which resulted in a manufacturing cost estimate of ca. \$66/lb for 3-FSA.

Our results from this work suggest that the Reimer-Tiemann reaction will allow one to manufacture 3-FSA with a manufacturing cost of from \$51-66/lb assuming, of course, the recycle of unreacted o-FP. This compares well with the previous reported manufacturing cost estimate of \$60/lb (8) for the more demanding four-step Claisen route. Whatever route is chosen, it must be kept in mind that development work will be required to achieve these results on a larger scale.

APPENDIX

EXPERIMENTAL PROCEDURES

Typical Reimer-Tiemann Reaction

The experimental procedure for the Reimer-Tiemann reaction involved the use of a 1-liter 3-necked glass R.B. flask equipped with a mechanical stirrer (stainless steel blade), thermometer and a condenser with a pressure equilibrating addition funnel on top. The o-FP (0.178 mole), toluene (214 ml) and base (NaOH, 1.01 mole) were mixed and brought to temperature with stirring. The alcohol (t-butanol, 36 ml) was added to the stirred mixture after it was at temperature for ca. 15-30 min. The alcohol addition considerably decreased the viscosity of the stirred suspension. With rapid stirring, the CHCl_3 was slowly added through the dropping funnel and the exothermic influence of the reaction on the reaction temperature was controlled with the use of either external cooling or heating. The first few drops of CHCl_3 caused the slurry color to change from white to pink. The pink color persisted only through the initial part of the addition step and was quickly followed by a yellow color which slowly darkened during the course of the reaction to a medium brown coloration by the time the reaction was terminated. At the end of the reaction period the mixture was cooled to ca. 20°C with the aid of an external ice bath. This mixture was then worked-up to obtain the 3-FSA and unreacted o-FP with either a base/acid or an acid method. The difference between methods will be discussed below.

Work-up; base/acid

Water was added to the cooled, alkaline reaction mixture followed by heating to distill off all the organic material (unreacted CHCl_3 , toluene, t-butanol, etc.) which did not form a sodium salt under these alkaline conditions. A

modified Dean-Stark trap was used to recycle the lower (water) layer. Upon completion of the removal of all possible organics through distillation the remaining mass was cooled to ca. 20°C and then acidified with HCl to a pH of 5-6. The 3-FSA and o-FP were then steam distilled into a modified trap which allowed continuous recycle of the upper (water) layer. The o-FP distilled first as a light green colored liquid followed by the 3-FSA which appeared as a white solid. When this phase of the distillation was complete, the distillation pot was further acidified to a pH of ca. 1 and again distilled to remove the last traces of 3-FSA and o-FP. This steam distillate (ca. 150 ml H₂O, 15g 3-FSA/o-FP) was then extracted with toluene (four times). The toluene was diluted to a calibrated volume, weighed and then evaluated by GC.

The GC method was also checked for accuracy by a work-up procedure which required more time but did afford an in-hand yield of the 3-FSA and also of the o-FP. In this case the steam distillate (ca. 150 ml H₂O, 15g 3-FSA/o-FP) was heated to 70°C with stirring and sufficient methanol (ca. 150 ml) was added to bring the melted 3-FSA into solution. The light green solution was then cooled to ca. 3-4°C to afford the near white colored 3-FSA which was then removed by suction filtration. The 3-FSA so obtained was found to contain from 10-13% water which was removed by use of either a vacuum oven or by dissolving the 3-FSA in a low-boiling solvent such as diethyl ether or hexane and drying the solvent followed by removal of solvent. The melting point of the 3-FSA so processed generally was in the 67-69°C range. The unreacted o-FP was obtained from the crystallization mother liquor by a procedure which involved first converting it to the sodium alkoxide to allow removal of water and methanol followed by acidification, extraction with toluene, drying and then distillation to afford the o-FP. The yields of recovered 3-FSA and o-FP were quite near (within ±5%) the yields reported by GC.

Work-up, acid

This work-up was similar to that discussed for the base/acid system except that on completion of the reaction the mixture was neutralized to pH 5-6 before removal of organic solvents. The distillation was then carried out with the aid of a vigreux column to first separate the organic solvent followed then by removal of the 3-FSA/o-FP mixture. This was done again with the aid of a modified Dean-Stark apparatus which allowed the recycling of the water portion. Before completing this distillation, the distillation pot material was acidified further to a pH of ca. 1 in order to remove the last traces of product. The remainder of the work-up and GC analysis was the same as that described for the base/acid work-up procedure.

GC Method

The GC method of analysis utilized a 1.5 meter X 5mm (ID) 5 wt% DC-550 on 30/60 mesh T-6 column run in a temperature program from 70°C to 250°C with an He flow rate of 60 ml/min. The GC method was calibrated with known mixtures prepared from the pure components and was found to be accurate with the in-hand method of analysis within $\pm 5\%$. The precision and accuracy of GC method was independently verified by our analytical service department.

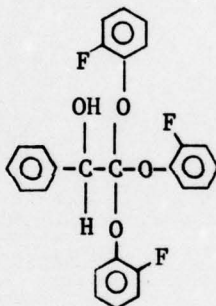
Reproducibility

Since most of the comments and conclusions put forth in this report are based on observations from single experiments, it is wise to discuss the results of an experiment run in triplicate to demonstrate the reproducibility of the work. Three experiments (Table 2, Expt. Nos. 41, 69 and 73) were with a reasonable range at 62-65% o-FP conversion and 28-30% 3-FSA yield. The duplicate runs suggest a good level of reproducibility.

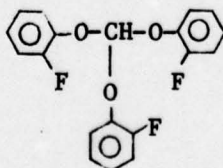
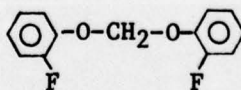
Analysis of Possible Intermediates

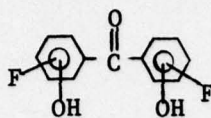
A few of the NaOH based reactions were run and stopped at various stages of the reaction in order to generate samples for evaluation by Mass Spec. It is possible that most of the active components of this system either had a short lifetime or that they were quite sensitive to their surroundings. Therefore it was difficult to quantify the amounts of these materials, however, a number of structures were identified which shed some light on the course of the reaction.

A major by-product recovered by filtration prior to the steam distillation of the o-FP/3-FSA mixture shown below is an orthoester which tied up 3 molecules of o-FP. This structure determination was based on NMR, MS and IR studies.



Other structures observed by Mass Spec evaluation of intermediate samples include such structures as shown below.





Most of these compounds are esters containing o-FP in a trapped, and probably less reactive (to :CCl_2) form which are readily hydrolyzed under acidic conditions to afford unreacted starting material. The presence of these intermediates would explain the less than 100% conversion of o-FP.

Possible Future Work

During the course of this investigation we have come across a few other possible methods with which we could ortho-formylate phenols. These methods are claimed to be rather ortho specific and would be worthy of further investigation if the manufacturing cost estimates for the Claisen and the Reimer-Tiemann methods are unacceptable. One of these approaches, the thioalkylation of a substituted phenol such as o-FP (16) was found to be quite selective but afforded low yields. Another approach which involved the reaction of a phenoxymagnesium halide with an excess of ethylorthoformate (17) afforded the desired ortho-hydroxyaldehyde. Finally, since more is also known about the Duff Reaction (18) and its formylation of the ortho position of phenols one could also investigate this route for 3-FSA.

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