RECENT DEVELOPMENTS IN FLUORINATION CHEMISTRY OF DAST WITH SPECIAL REFERENCE TO ALCOHOLS

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Dedicated to late Prof. V. N. Pathak

Abstract

Fluorine containing organic compounds have influenced both medicinal and agrochemical fields. The presence of fluorine or a fluorine containing group causes notable changes in the physical and chemical properties of ordinary organic compounds. The most significant method to introduce fluorine into organic compounds is the nucleophilic replacement of oxygen with fluorine. Diethylaminosulfur trifluoride (DAST), Bis(2-methoxyethyl)aminosulfur trifluoride (BAST) or deoxofluor are the popular fluorinating reagents. By the use of these reagents, organic compounds that contain oxygen in hydroxyl and carbonyl groups are readily converted into their corresponding fluorinated analogues by the introduction of one or two fluorine atoms respectively. Our interest in applying various synthetic methods to incorporate fluorine or a fluorinated group into a large variety of organic compounds encouraged us to summarize the recent chemistry of DAST.

Keywords: Agrochemical; Diethylaminosulfur trifluoride (DAST); Bis(2-methoxyethyl)aminosulfur trifluoride (BAST); Fluorinated analogues

1. INTRODUCTION

Fluorine is the most electronegative element. Therefore, fluorine or a fluorine containing group into organic molecules cause changes in their physical, chemical and biological properties and makes them suitable for diverse applications in agricultural\textsuperscript{2} and pharmaceutical fields\textsuperscript{3}. The carbon-fluorine bond gives more stability to the organic molecules besides enhancing its lipophilicity\textsuperscript{4}. This review highlights the recent progress in fluorination reactions of alcohols using diethylaminosulfur trifluoride (DAST) as key nucleophilic fluorinating reagent.

Several reviews\textsuperscript{5-8} in this area in the last few years have been compiled and the most recent of these have been included.

Diethylaminosulfur trifluoride is a useful selective and multipurpose activating reagent for replacing oxygen with fluorine in organic compounds under very mild conditions\textsuperscript{9,10}. The ready availability of molecules, low cost and stability makes it very desirable in selective fluorination and cross-coupling reactions. DAST was introduced as a mild and selective reagent.
by Middleton et al.\textsuperscript{11,12} for the conversion of primary, secondary, tertiary alcohols to fluorides; aldehydes and ketones to difluorides; carboxylic acids to acyl fluorides and sulfoxides to $\alpha$-fluorosulfides. The structure of DAST and its NMR studies have also been reported earlier\textsuperscript{13,14}.

Keeping all these observations in mind and in continuation to our other work on organo-fluoro compounds\textsuperscript{15,16} we have compiled the fluorination reactions of DAST with special reference to alcohols.

2. SYNTHESIS AND PROPERTIES OF DAST

DAST \textsuperscript{2} have been prepared by the treatment of sulfur tetrafluoride with diethylaminotrimethylsilane \textsuperscript{1} and separated from the volatile trimethylfluorosilane by distillation Fig. 1.

\[
\begin{align*}
\text{SF}_4 + (C_2H_5)_2NSi(CH_3)_3 & \quad \xrightarrow{\text{CCIF}} \quad (C_2H_5)_2NSF_3 + FSi(CH_3)_3 \\
1 & \quad \text{-65° to -60° r. temp} & \quad 2 & \quad 3
\end{align*}
\]

Fig. 1. : Synthesis of DAST

When this reaction is conducted in trichlorofluoromethane (b.p. 25°c) at –70°c, high yield products are obtained with very high purity since the only appreciable by product is fluorotrimethylsilane \textsuperscript{3} which is an early separated low boiling (b.p. 17°c) material.

Reaction mechanism of DAST with alcohol is presented in Fig. 2.

\[
\begin{align*}
\text{ROH} + \text{F}_3\text{SN(CH}_2\text{CH}_3)_2 & \quad \xrightarrow{} \quad \text{RO} \quad \text{S} \quad \text{N(CH}_2\text{CH}_3)_2 \\
4 & \quad 5 & \quad 6 & \quad [\quad R + \quad \text{O} \quad \text{S} \quad \text{N(CH}_2\text{CH}_3)_2 \\
7 & \quad \text{R} & \quad \text{O} & \quad \text{S} & \quad \text{N(CH}_2\text{CH}_3)_2 \\
8 & \quad \text{RF} & \quad \text{HO} & \quad \text{S} & \quad \text{N(CH}_2\text{CH}_3)_2 \\
9 & \quad \text{RF} & \quad \text{HO} & \quad \text{S} & \quad \text{N(CH}_2\text{CH}_3)_2
\end{align*}
\]

Fig. 2. : Reaction Mechanism of Diethylamino sulfur trifluoride
Several other methods have also been reported for preparation of diethylaminosulfur trifluoride \(^{17,18}\) Fig. 3.

\[
\begin{array}{c|c|c|c}
\text{(C}_2\text{H}_5\text{)}_2\text{NSOF} & 10 & 2\text{SF}_4 & (97-98\%) \\
\text{(C}_2\text{H}_5\text{)}_2\text{NSO}_2\text{C}_2\text{H}_5 & 11 & 2\text{SF}_4 & (55-68\%) \\
\text{(C}_2\text{H}_5\text{)}_2\text{NSON(C}_2\text{H}_5\text{)}_2 & 12 & 3.3\text{SF}_4 & (90-98\%) \\
\text{(C}_2\text{H}_5\text{)}_2\text{NSOC}_6\text{H}_4\text{CH}_3\text{-P} & 13 & 1.5\text{SF}_4 & (65-70\%) \\
\end{array}
\]

\[
\text{20-25° autoclave} \quad 12\text{h} \quad \rightarrow \quad \text{(C}_2\text{H}_5\text{)}_2\text{NSF}_3 \quad 14
\]

**Fig. 3 : Other methods for preparation of DAST**

Although several other dialkylaminosulfur trifluorides have been prepared \(^{19}\) but most of the work has been done with DAST. Some difficulties are associated with DAST as it decomposes at 90°C and can explode if heated at higher temperatures and it is hazardous if not properly handled \(^{20-22}\). DAST can be distilled and stored in plastic bottles at room temperature. Most reactions with DAST can be carried out in conventional glass wares at room temperature. DAST requires special handling because it is flammable and reacts violently with water. The boiling point of DAST is 43-44°/12 min and its density is 1.4125.

DAST has found widespread utility in the fluorination of alcohols, aldehydes, ketones, polyfunctional molecules such as cephalosporins, carbohydrates, proteins, steroids, terpenoids, glycosides and peptides.
3. FLUORINATION REACTIONS OF DAST

Reactions of DAST with organic compounds are summarized as follows Fig. 4.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCO₂H → RCOF (+RCF₃)*</td>
<td>20 21 22</td>
</tr>
<tr>
<td>RSO₂H → RSO₂F</td>
<td>23 24</td>
</tr>
<tr>
<td>R₂P(O)OH → R₂P(O)F</td>
<td>25 26</td>
</tr>
<tr>
<td>RCOCl → RCOF</td>
<td>27 28</td>
</tr>
<tr>
<td>RSOCl → RSOF</td>
<td>29 30</td>
</tr>
<tr>
<td>RSO₂Cl → RSO₂F</td>
<td>31 32</td>
</tr>
<tr>
<td>R₃SiCl → R₃SiF</td>
<td>33 34</td>
</tr>
<tr>
<td>ROSiR₃ → RF</td>
<td>35 36</td>
</tr>
<tr>
<td>RCH(OR¹)SR² → RCH(OR¹)F</td>
<td>37 38</td>
</tr>
<tr>
<td>RCH₂S(O)R¹ → RCH(OR¹)F</td>
<td>39 40</td>
</tr>
<tr>
<td>(C₆H₅PO/(C₆H₅)₃PS → (C₆H₅)₃PF₂</td>
<td>41 42</td>
</tr>
</tbody>
</table>

Fig. 4: Reactions of DAST with organic compounds

3.1 FLUORINATION OF ALCOHOLS

DAST 2 was used to convert the hydroxyl group into corresponding monofluorides at 25°C but in some cases either higher or lower temperatures were also used. Primary, secondary, tertiary, allylic and benzylic alcohols are converted into corresponding fluorides in high yields. Carbocation rearrangements occur although to a lesser extent than other fluorinating agents.

A rearrangement occurs when non-racemic indolylhydroxypiperidine-1-carboxylic acid ester 43 and 45 are treated with DAST to afford non-racemic indolylfluoropiperidine-1-carboxylate 44 and 46 with complete regio- and stereoselectivity with 91% ee after debenzoylation Fig. 5.
Fig. 5: Fluorination of hydroxyl containing piperidine ring with DAST

The selective fluorination of hydroxyketones into fluoroketones has also been accomplished viz. transformation of hydroxyketosteroids into fluoroketosteroids by treatment with DAST at room temperature has also been noticed30-32.

1-(5-chlorobenzoxazol-2-yl)-1-(4-fluoro-3-trifluoromethylbenzyl)propanol fluorinated with DAST in CH₂Cl₂ at 50°C to yield the corresponding 1-(5-chlorobenzoxazol-2-yl)-1-(4-fluoro-3-trifluoromethylbenzyl) propyl fluoride in 88% yield33.

Treatment of (2S,3S)-methyl-3-benzyloxy-2-hydroxytetradec-6-enoate 47 with DAST afforded (2R,3S)-methyl-3-benzyloxy-2-fluorotetradec-6-enoate 4834 Fig. 6.

Fig. 6: Fluorination of (2S,3S)-Methyl-3-benzyloxy-2-hydroxytetradec-6-enoate

A series of unsaturated ω-fluoroalcohols have been prepared stereoselectively with DAST. These simple compounds are structural analogues of the trail pheromone of termites in the genus reticulitermes35. Trans-3-hydroxy-4-(2-oxopyrrolidin-1-yl)benzopyrans have been shown to undergo inversion to cis-3-hydroxy-4-(2-oxopyrrolidin-1-yl)benzopyrans on treatment with DAST36.

Fluorination of secondary alcohols vicinal to an arene Cr(CO)₃ unit with DAST gives the corresponding fluorides37 with very high exo stereoselectivity.
Fluorination of chiral propargylic alcohols with DAST gives high stereoselective propargylic fluorides Fig. 7\textsuperscript{38,39}.

![Chemical structure diagram]

**Fig. 7: Fluorination of chiral propargylic alcohols**

Treatment of 1,1-difluoro-1-alken-3-ols with DAST afford (E)-1,1,1-trifluoro-2-alkens with high regio and stereoselectivity\textsuperscript{40,41}.

Treatment of 1,1-difluoro-1,4-dien-3-ol by DAST yielded (E,E)-8,10-dodecadienol (Codlemone)\textsuperscript{42} 54 Fig. 8.

**HO(CH\textsubscript{3})\textsubscript{7} = CF\textsubscript{3}**

**Fig. 8: Fluorination of 1,1-difluoro-1,4-dien-3-ol**

1-Nonylcyclobutanol reacts with DAST to give a 1-fluoro-1-nonylcyclobutane\textsuperscript{43}. Blackburn et al.\textsuperscript{44} have reported the novel synthesis of α- and γ-fluoroalkyl-phosphonates with DAST. The fluorination of DAST with 3- nonyne-2-ol or 1-dodecyne-3-ol, both in racemic and optically active form has been investigated\textsuperscript{45}. Treatment of (+)-(S)-2-octanol with DAST affords (-)-R-2-fluoroctane along with octane\textsuperscript{46} Fig. 9.

**Fig. 9: Fluorination of (+)-(S)-2-octanol**

Reaction of steroidal 17-acetylenic alcohols with DAST affords C-17 β-fluoro derivatives\textsuperscript{47}. Lakshmipathi et al.\textsuperscript{48} showed that DAST promotes an unusually easy C-C bond cleavage when epoxy alcohols are used, leading exclusively to monofluoro vinyl ethers Fig. 10.
Induced 1,2-migration occurs via a proposed spiroaziridinium intermediate when 1-phthaloylamino-3-[4-(2-methoxyphenyl)piperazin-1-yl]propanol is treated with DAST to afford N-[2-fluoro-3-(4-(2-methoxyphenyl)piperazin-1-yl)propyl] phthalimide in 13% yield and N-[2-fluoromethyl-2-(4-(2-methoxyphenyl)piperazin-1-yl)ethyl] phthalimide in 73% yield.

The (R)-decynol 63 was transformed into the (S)-4-fluoro-1-decyne 64 and the (S)-decynol 65 was converted into the (R)-4-fluoro-1-decyne 66 with DAST.

DAST reacts with dialcohols to give difluoride sulfite esters or cyclic ethers depending on the number of carbons separating the two alcoholic groups.

A series of 1,1-bis(indol-3-yl) and 1-(indol-2-yl)-1-(indol-3-yl)-ω-hydroxyalkanes have been prepared from the corresponding indole derivatives and suitable hydroxyaldehydes via routine coupling reactions with DAST under mild conditions.

Bis(spirodienol) derivative 67 reacts with DAST to give fluorinated calixarenes 68, 69.
1,1-Bis(trifluoromethyl) substituted olefins are prepared by treatment of 1,1-difluoro-2-trifluoromethyl-1-alken-3-ols with DAST with high regioselectivity. Ionic liquids are reported as recyclable solvents for DAST mediated fluorination of alcohols.

Fig. 12: Fluorination of bis (spirodienol) derivative with DAST

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Fluorination of Ionic liquids

Piyasena et al.\textsuperscript{56,57} and Dischino et al.\textsuperscript{58} have prepared 3-fluoro-3-phenyloxindole derivatives 74 on fluorination with DAST in 93% yield which act as modulators of KCNQ potassium channels for treatment of migranes Fig. 14.

![Fluorination of Ionic liquids](image)

**Fig. 13: Fluorination of Ionic liquids**

Fluorination of oxazolidine substituent containing alcohols 75a,b with DAST produced the corresponding monofluoro derivatives 76a,b with inverted configuration. Cleavage of the oxazolidine ring of the monofluoro derivatives and deprotection of t-Boc group with trifluoroacetic acid gave the L-threo-3-fluorosphinganine analogues 77a,b in good yields Fig. 15\textsuperscript{59}.

![Fluorination of tertiary hydroxyl groups in oxindole derivatives](image)

**Fig. 14: Fluorination of tertiary hydroxyl groups in oxindole derivatives**

Fluorination of oxazolidine substituent containing alcohols 75a,b with DAST produced the corresponding monofluoro derivatives 76a,b with inverted configuration. Cleavage of the oxazolidine ring of the monofluoro derivatives and deprotection of t-Boc group with trifluoroacetic acid gave the L-threo-3-fluorosphinganine analogues 77a,b in good yields Fig. 15\textsuperscript{59}.

![Fluorination of hydroxyl group in substituted oxazolidine rings with DAST](image)

**Fig. 15: Fluorination of hydroxyl group in substituted oxazolidine rings with DAST**
1-Methyl-3-hydroxy-5-phenyl-7-chloro-1,3-dihydro-2H-1,4-benzodiazepin-2-one was treated with DAST in CH₂Cl₂ at ≤50°C to give 78 where R=H, R¹=Cl, R²=Me, Z=0 Fig. 16⁶⁰,⁶¹.

![Chemical structure of 78](image)

**Fig. 16: Fluorination of 1-methyl-3-hydroxy-5-phenyl-7-chloro-1,3-dihydro-2H-1,4-benzodiazepin-2-one**

Treatment of DAST with diarylcarbinols 79 yields bis(diarylmethyl)ethers 80⁶² Fig. 17.

![Chemical structures of 79 and 80](image)

**Fig. 17: Fluorination of diarylcarbinols**

Substituent effects on the regioselectivity in fluorination of allylic alcohols with DAST have also been reported⁶³. Reactions of various phosphonate derivatives with DAST were reported⁶⁴-⁶⁶ to give the corresponding monofluoride derivatives which were claimed to be reactive immunization agents towards the hydrolysis of organophosphorus nerve agents Fig. 18⁶⁷.
DAST also reacts with hydroxyl group of benzoylamino benzopyrans. Treatment of α-hydroxyphosphonates with DAST affords α-fluorophosphonates. Fluorination of rhenium complex 87 with DAST yielded 40% allylic fluoride complex Fig. 19.
A convergent approach for the synthesis of fluorinated sphingosine analogues with DAST have also been reported\(^7\). Fluorination of L-glucodiol with DAST followed by treatment with AcOH lead to the D-ido-fluorohydrin\(^7\). Fluorination of 2-hydroxyalkylazetidines with DAST gives 3-fluoropyrrolidines\(^7\). Theoretical studies have also been done on fluorination mechanism of 2-hydroxy-3-phenylalkanoate with DAST\(^7\). DAST-mediated conversions have also been done of a range of alcohols to the corresponding fluorides in microreactors\(^7\) Fig. 20.

Conversion of \(\alpha\)-hydroxyl group into fluorine was achieved by the reactions of \(\alpha\)-hydroxybenzylphosphonate with DAST in dichloromethane to give diethyl \(\alpha\)-fluorobenzylphosphonate in 53% yield\(^7\).

### 3.2 General Reaction Mechanisms for Fluorination of Alcohols Using DAST

DAST involves the nucleophilic displacement of fluorine on sulfur by oxygen of the hydroxyl group through elimination of hydrogen fluoride.

\[
\text{ROH} + \text{F}_3\text{SNR}_2 \rightarrow \text{ROSF}_2\text{NR}_2 + \text{HF}
\]

\[
\text{ROSF}_2\text{NR}_2 + \text{F}^- \rightarrow \text{R-F} + \text{FSONH}_2 + \text{F}^-
\]

Generally, intermediate \(91\) is converted into alkyl fluoride \(92\) by reaction with fluoride.
β-Diketones exist in keto 93 and enol 94 forms, when fluorination occurs, the enol form 95 react with one molecule of DAST and the hydroxyl group was replaced by fluorine. An α-fluoro derivative 96 was generated during the reaction which also existed in equilibrium with the enol form 97. Another molecule of DAST fluorinated with 97 to give α,β-difluoro product 99 as a mixture of E and Z isomers in 1:1 ratio. Fig. 22.

**Fig. 22: Reaction mechanism for fluorination of β-diketones with DAST**

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