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Preparation and Reactions of Aliphatic 2-Pentafluorosulfanyl Aldehydes

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A facile preparation of aliphatic 2-pentafluorosulfanyl aldehydes is described. To investigate the utility of the aldehydes as synthetic building blocks, various transformations of the aldehydes were explored. The pentafluorosulfanyl group

was stable under a variety of reaction conditions, and the pentafluorosulfanylated products were obtained in moderate to good yields in most cases.

Introduction

The growing importance of pentafluorosulfanylated aromatic compounds is demonstrated by their utility in liquid crystalline displays,^[1] in agrochemicals,^[2] and in medicinal chemistry.^[3] To date, the chemistry of aliphatic pentafluorosulfanylated compounds has been much less well explored, in part, because of a paucity of available building blocks or synthetic methods to construct these compounds.^[4] To address this shortcoming, a general synthesis of pentafluorosulfanylated (SF₅) aliphatic aldehydes was developed and the reactivities of these materials were compared with the corresponding trifluoromethylated analogs.

The preparation of SF₅-containing aliphatics^[4a] is principally effected by SF_5X (X = Cl or Br) addition across multiple bonds. Case^[5] first incorporated the SF₅ group into hydrocarbons by treating SF5Cl with olefins under free-radical conditions. Gard subsequently studied the addition of SF₅X to acrylates, allylic esters, and fluorinated alkenes by using standard thermal and/or photochemical conditions,^[4a,6] but it was Dolbier's utilization of triethylborane to promote addition reactions of SF5X that was the crucial advance in this chemistry.^[4b,7]

By analogy to the addition of perfluoroalkyl iodide to vinyl acetate,^[8] Gard reported the successful addition of SF₅Cl and SF₅Br to vinyl acetate under pressure.^[4a,6a] The conversion of chloroacetate 2a to parent aldehyde 3 was successful, but the product usually exists as a hydrate.^[9] In the presence of powdered P₄O₁₀, trimer 4 formed readily (Scheme 1).^[10] However methanolysis of 2a led to formation of ketal 5 that was readily oxidized to methyl ester ${\bf 6}$ (Scheme 2). $^{[4b]}$ Those are the only reports about the 2pentafluorosulfanylated aliphatic aldehydes. The general synthesis and the reactivity of these compounds are interesting but still remain to be addressed.



Scheme 1. Synthesis of SF₅-acetaldehyde.



Scheme 2. The oxidation of ketal 5.

Results and Discussion

We found that with Et₃B initiation, SF₅Br adds easily to enol acetates, prepared by using either isopropenyl acetate with *p*-toluensulfonic acid^[11] or a mixture of potassium acetate and acetic anhydride,^[12] to form bromo-SF₅-acetates 8 as a 3:1 mixture of diastereomers (Scheme 3).



Scheme 3. Addition of SF₅Br to enol acetates.

SF₅Br addition was effected quickly under mild conditions (0 °C, 20 min).^[4c] Formation of 8 was accompanied by less than 10% of the ionic addition product of bromo-

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fluorination 8'. The attempted reactions of more hindered enol acetates such as that derived from isovaleraldehyde, or of the enol acetate derived from phenylacetaldehyde, where the intermediate cation formed by electrophilic addition can be stabilized by the adjacent aromatic ring, primarily gave the ionic addition products.

Pentafluorosulfanyl bromoacetates **8** were easily converted into dimethyl acetals **10** or hydrolyzed directly into α -SF₅-aldehydes **9**. Dimethyl acetals **10** resulting from heating under reflux with methanol can easily be hydrolyzed to **9** (Scheme 4).^[13] Alternatively, direct hydrolysis of **8** by using a mixture of hydrochloric acid and glacial acetic acid is efficient.^[12] Attempts to use milder conditions with lithium halide or metal oxide salts were not effective.^[14] The lower yield of 2-pentafluorosulfanylpentanal **9a** (<30%) was attributed to mechanical losses as a result of the volatility of the compound. There was evidence of some spontane-



Scheme 4. The preparation of aldehydes.

ous debromoacetylation during normal workup following SF_5Br addition; however, attempts at steam distillation of the product under nonacidic conditions resulted in incomplete conversion into **9** (Scheme 4).^[15] In contrast to the propensity of parent aldehyde **3** to trimerize,^[10] the higher molecular weight aldehydes were easily handled and, thus, were subjected to additional transformations.

Little has been reported about the reactions of SF_5 -containing aldehydes, yet 9 underwent many of the common reactions of aldehydes easily (Scheme 5). Reduction with sodium borohydride gave the corresponding primary alcohols 11. The generally high yields of this process are indicative of the stability of the SF_5 group to the reaction conditions.

Nucleophilic addition to the carbonyl group by using organolithium or Grignard reagents, as anticipated, gave the corresponding alcohols **12** with high diastereoselectivity (>99%). In contrast to decomposition that occurred upon the exposure of aromatic SF₅-compounds to *n*-butyllithium,^[16] the aliphatic SF₅ group was observed to be quite robust.

The addition of nonsterically demanding methyllithium or vinylmagnesium bromide was highly diastereoselective; only a single diastereomeric pair was observed by NMR spectroscopy, or a diastereomer ratio of at least 20:1. By analogy to the reactions of trifluoromethyl aldehydes such as 3,3,3-trifluoropropanal, *ul* attack was predicted as with **B** (Figure 1).^[17] The *ul* attack was favored in reactions with a nonsterically demanding nucleophile in only a 2.6:1 ratio.^[17] In reactions of **9b**, addition to either conformation



Scheme 5. Reactions of α -SF₅-aldehydes.

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C or **D** of the α -SF₅-aldehydes would lead to the same *ul* stereochemical outcome. The remarkably large C–SF₅ bond dipole moment may contribute to the relative importance of the Cornforth conformation^[18] **D** in the additions and may amplify the diastereoselectivity of the process observed in reactions of α -SF₅-aldehydes **9**.



Figure 1. Diastereoselectivity of addition to α -SF₅-aldehydes.

The failure to observe coupling between H^a and H^b is consistent with a product conformation where the H^a-H^b torsional angle is near 90°. On this basis alone it is not possible to establish the relative stereochemistry of the vinyl alcohol. However, the clear evidence of a NOE between H^c and the pentyl substituent is in accord with the proximity of H^c to the first methylene of the pentyl chain in **E**. For the product diastereomer to be *lk* diastereomer **F** the experimentally determined NOE and coupling requires the molecule to assume a highly unfavorable conformation. The vinyl group would be required to be simultaneously *gauche* to both the SF₅ group and the pentyl chain, a conformation that also precludes the favorable hydroxy SF₅ interaction.

The acidity of aldehyde 9 could be obviated by the careful choice of the carbanion nucleophile. The addition of trimethylsilylmethyllithium to 9c proceeds smoothly to yield alcohol 12f (Scheme 5). Subsequent treatment of 12f with BF₃·OEt₂ yielded olefin **13f**. However the Wittig reagent, methylene triphenylphosphane, gave no olefination reaction, only products of decomposition. In contrast, the more nucleophilic Horner-Wadsworth-Emmons reagent prepared from triethyl phosphonoacetate reacted efficiently and exclusively to form predicted E alkenes 14. Whereas dimethylsulfonium ethoxycarbonlymethylide formed epoxide 15, neither the dimethylsulfonium methylide, diphenylsulfonium cyclopropylide, or dimethylsulfoxonium methylide reacted cleanly with aldehyde 9.

With ready access to α -SF₅-aldehydes, direct oxidation to the carboxylic acids was an appealing transformation. The successful conversion of dimethyl acetal **5** into methyl ester

6 is known.^[4b] Unfortunately, the preparation of 2-halo-2pentafluorosulfanyl carboxylic acids **16e** and **16f** by successive addition of SF₅Cl to methoxy- or ethoxyethyne or propyne followed by halogenation and hydrolysis (Figure 2)^[19] required either the use of pressure or low temperature photolysis. Those results were predicated on even earlier work from the same group that involved hydrolysis of a SF₅Cl ketene adduct.^[20] Surprisingly, attempts to effect oxidation of **9** under mild conditions such as with the use of Ag₂O^[21] gave no reaction. Fortunately, simple treatment with KMnO₄ or NH₂SO₃H/NaClO₂ readily formed the corresponding carboxylic acids **16a** and **16c** (Scheme 5).

$$R^{1}_{X} \rightarrow CO_{2}H_{SF_{5}}$$
16e: R¹ = H, X = Br
16f: R¹ = CH₃, X = Br

Figure 2. 2-Halo-2-SF5-carboxylic acids.

Conclusions

An efficient method for the preparation of aliphatic 2pentafluorosulfanyl aldehydes was developed. Various transformations of aldehydes proceeded smoothly to give the products in moderate to good yields. The nucleophilic addition to the carbonyl group showed excellent diastereoselectivity that can be readily rationalized. Peterson olefination and Horner–Wadsworth–Emmons olefination afforded the alkene in moderate yields. The epoxidation of the aldehyde with dimethylsulfonium ethoxycarbonlymethylide also went well. With careful selection of the oxidant reagent, the oxidation gave the product in excellent yield. Further studies on the chemistry of aliphatic pentafluorosulfanylated compounds are currently underway.

Supporting Information (see footnote on the first page of this article): General procedures, characterization data, and NMR spectra for compounds synthesized.

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Aldehyde Tranformations

An efficient method to prepare aliphatic 2pentafluorosulfanyl aldehydes was developed. An investigation of various aldehyde transformations showed that the pentafluorosulfanyl group was stable under a variety of reaction conditions, and the products were obtained in moderate to good yields.



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