# *gem*-Difluoro Compounds: A Convenient Preparation from Ketones and Aldehydes by Halogen Fluoride Treatment of 1,3-Dithiolanes

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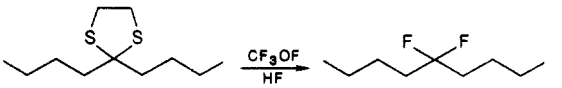
*Received May 20, 1986*

*gem*-Difluoro compounds can be prepared from ketones and aldehydes by formation of the corresponding 1,3-dithiolanes, followed by reaction with 1,3-dibromo-5,5-dimethylhydantoin and pyridinium poly(hydrogen fluoride) (HF–pyridine) in methylene chloride. The reaction requires 2 equiv of $Br^+$ and appears to proceed through a sequence of two bromosulfonium ions that open and cleave, respectively, to sulfur- and fluorine-stabilized carbocations that are trapped by fluoride ion. Formation of *gem*-difluoro compounds from dithiolanes derived from ketones is efficient and rapid, even at −78 °C, whereas reaction of dithiolanes derived from aldehydes proceeds rapidly only at higher temperature (0 °C). While the reaction operates successfully on a variety of ketones and aldehydes, brominated byproducts are observed with electron-rich aromatic systems, and side reactions take place in systems prone to carbonium ion rearrangements. The successful geminal difluorination of the related 1,3-dithiane system, although slower than the 1,3-dithiolanes, makes the former system a synthetic equivalent to the difluoromethyl 1,1-dianion. The two-step geminal difluorination of ketones and aldehydes by treatment of the 1,3-dithiolanes with halogen fluoride is a convenient alternative to the use of sulfur tetrafluoride: It is efficient, proceeds at low temperatures, and can be carried out in conventional glassware.

The preparation of compounds containing *gem*-difluoro groups has been of interest to both physical chemists and biochemists, since the *gem*-difluoro group has a steric profile similar to that of the methylene group but has a very different polarity and a drastically altered reactivity.[1] The *gem*-difluoro group is prepared, most frequently, from the corresponding carbonyl compound, a ketone or aldehyde; however, this approach is often limited by the inconvenience of obtaining and using the reagents required for this conversion. Sulfur tetrafluoride with hydrogen fluoride as a catalyst, the classical method for achieving this transformation,[2] generally provides good yields of the desired product, but its use requires extreme caution because of its toxicity, reactivity, and volatility (bp −40 °C); pressure equipment constructed of fluorine-resistant material such as "Hastelloy-C" bombs[3] must be used, and high temperatures are frequently necessary. The conversion of carbonyl compounds to *gem*-difluoro groups can also be accomplished with selenium tetrafluoride, (diethylamino)sulfur trifluoride (DAST), phenylsulfur trifluoride, and molybdenum hexafluoride. Of these reagents, only DAST is consistently commercially available,[4] and its use requires vigorous conditions for most ketones and aldehydes.[5,6] Erratic results have been obtained with the sporadically available $SeF_4$.[7,8] Although requiring only mild reaction conditions, molybdenum hexafluoride (also sporadically available)[7] provides low yields and is difficult to use because of its volatility.[9] Phenylsulfur trifluoride, not available commercially, gives good yields but usually requires elevated temperatures.[10]

Fluorodesulfurization, a fluorination method developed by Kollonitsch and Marburg,[11] suggested an interesting new approach. They found that treatment of thiols with $F_2$, trifluoromethyl hypofluorite ($CF_3OF$), or *N*-chlorosuccinimide, with liquid HF as the solvent, led to cleavage of the carbon–sulfur bond and formation of a carbon–fluorine bond. Their suggested mechanism involved the formation of an oxidized sulfur species as a leaving group, with solvent HF being the source of fluorine for the carbon–fluorine bond. While tertiary thiols reacted with all three reagents, displacement of primary thiols required $F_2$, the most reactive oxidant, because a more highly oxidized state of sulfur was needed to be effective as a leaving group at the primary carbon center. Although Kollonitsch and Marburg did observe the formation of 5,5-difluorononane (**2**) from the treatment of 2,2-di-*n*-butyl-1,3-dithiolane (**1**)




**1** **2** (50%)

with $CF_3OF$ in HF, we believed that dithiolanes might be fluorinated under much milder conditions, since the carbonium ion intermediates from this system would be highly stabilized, first by sulfur and then by fluorine.

Recently, Nicolaou and co-workers have reported the conversion of (phenylthio)glycosides to glycosyl fluorides by treatment with *N*-bromosuccinimide (NBS) and DAST.[12] Nicolaou states that pyridinium poly(hydrogen fluoride) can also be used as the fluoride source,[12] although no experimental details are provided. This result supports our belief that very mild conditions may be suitable for fluorination of systems that proceed through highly stabilized carbonium ion intermediates. Thus, we chose to examine milder oxidants and a more convenient source of fluoride ion to effect the geminal difluorination of dithiolanes.

In this report we describe the facile reaction of 1,3-dithiolanes **4** with N-halo compounds and pyridinium poly(hydrogen fluoride) to form the corresponding *gem*-difluoro compounds **5**. Since the dithiolanes can be prepared readily from the corresponding aldehydes and ketones **3**, the overall two-step process represents a conven-

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(2) Boswell, G. A.; Ripka, W. C.; Scribner, R. M.; Tullock, C. W. *Org. React. (N.Y.) 1974, 21*, 20–30.
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(4) Available from Aldrich.
(5) Boulton, K.; Cross, B. E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1354–1357.
(6) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578.
(7) Occasionally available from Ozark-Mahoning.
(8) Kent, P. W.; Wood, K. R.; British Patent 1 136 075, 1968.
(9) Mathey, F.; Bensoam, J. *Tetrahedron* **1971**, *27*, 3965–3969.
(10) Sheppard, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 3058–3063.
(11) Kollonitsch, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1976**, *41*, 3107–3111.
(12) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189–4192.

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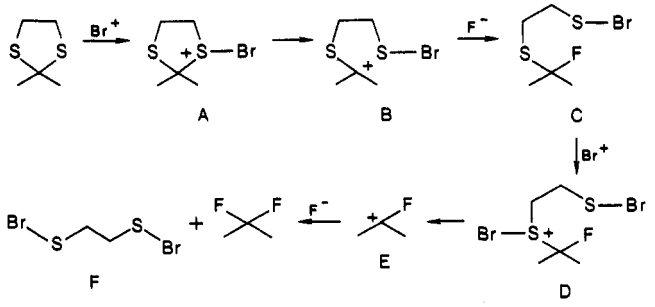
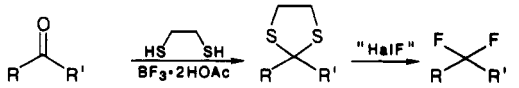
**Scheme I**




ient method to convert aldehydes and ketones to *gem*-difluoro compounds.




**3a** (R,R' = $n$-$C_5H_{11}$) **4a** **5a**
**3b** (R = H, R' = $C_{11}H_{23}$) **4b** **5b**

## Results and Discussion

**Generation of Halogen Fluorides.** It is believed that N-halo compounds combine with hydrogen fluoride to generate halogen fluorides in situ.[13,14] The halogen fluorides BrF and IF have been used in a variety of selective fluorination reactions;[13] the more reactive ClF[18] is generally less selective and, therefore, less useful. The recent commercial availability of pyridinium poly(hydrogen fluoride) as a source of HF makes the preparation of halogen fluorides particularly convenient,[19] since it can be used in conventional laboratory glassware.

**Preparation of 1,3-Dithiolanes.** We have prepared dithiolanes by a variation of Fieser's[20] method, employing boron trifluoride–acetic acid complex ($BF_3$·2HOAc) both as the condensing agent and the solvent. The formation of the dithiolane was effected by adding the ketone (or aldehyde) to a twofold excess of 1,2-ethanedithiol and 1 equiv of $BF_2$·2HOAc, stirring under nitrogen for 15–30 min. The dithiolane can be isolated and purified by flash chromatography (or recrystallization, in appropriate cases).

***gem*-Difluoro Compounds from 1,3-Dithiolanes. Presumed Mechanism and Investigation and Optimization of General Reaction Characteristics.** When 2,2-dipentyl-1,3-dithiolane (**4a**), the dithiolane derived from 6-undecanone (**3a**), was allowed to react with an excess of 1,3-dibromo-5,5-dimethylhydantoin (DBH) and pyridinium poly(hydrogen fluoride) in $CH_2Cl_2$ at −78 °C, an 83% yield of 6,6-difluoroundecane (**5a**) was obtained after only 5 min.

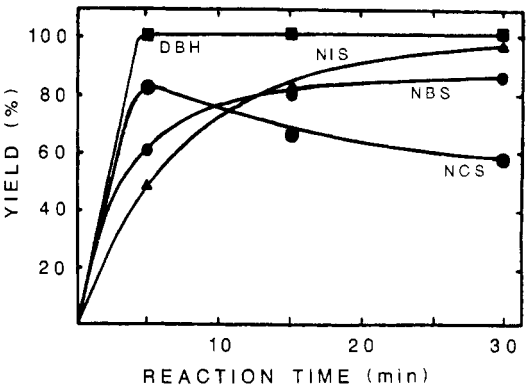



**Figure 1.** Time course of formation of 6,6-difluoroundecane (**5a**) from 2,2-dipentyl-1,3-dithiolane (**9a**) with different N-halo oxidants. The dithiolane **4a** was treated with 5 equiv of the indicated N-halo compound and 2 equiv of fluoride (as HF–pyridine) in $CH_2Cl_2$ at −78° C. At the indicated times, an aliquot was removed, diluted with hexane, filtered through basic alumina, and analyzed by GLC. Quantitation was achieved by use of $n$-decane as an internal standard.

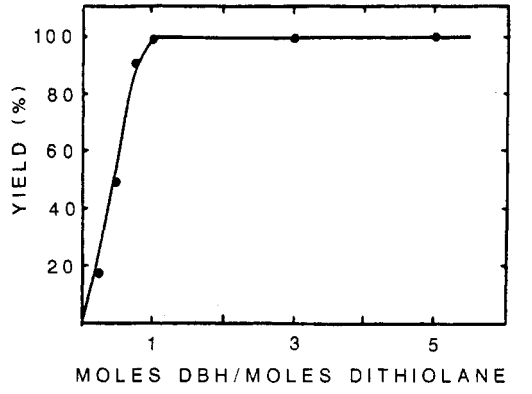



**Figure 2.** Yield of 6,6-difluoroundecane (**5a**) from 2,2-dipentyl-1,3-dithiolane (**4a**) as a function of the mole ratio of DBH to **4a**. Each reaction combined 0.4 mmol of dithiolane **4a**, 20 equiv of fluoride (as HF–pyridine) and DBH (0.1–5.0 mmol) in $CH_2Cl_2$ at −78 °C. After 10 min, an aliquot was removed, diluted with hexane, filtered through basic alumina, and analyzed by GLC. Quantitation was achieved by use of $n$-decane as an internal standard.

One may presume that this reaction proceeds according to the sequence shown in Scheme I. Attack of $Br^+$ on the dithiolane produces bromosulfonium intermediate A, which opens up to give sulfur-stabilized carbocation B that is captured by fluoride ion. A second equivalent of $Br^+$ then attacks C, again forming bromosulfonium ion D that cleaves to give fluorine-stabilized carbocation E, which, in the final step, captures fluoride, forming the *gem*-difluoro compound. The reaction byproduct would be 1,2-ethanebis(sulfenyl bromide) (F) or some species of equivalent oxidation state. Carbocations are stabilized by fluoride substitution but less so than by carbon or sulfur substitution.[21] Therefore, the second, fluorine-substituted carbocation E will be less stable than the first, sulfur-substituted one B, and, presumably, formation of carbocation E will be the rate-limiting step of the reaction sequence.

Temperature is an important factor in the dithiolane reaction with halogen fluoride. At −78 °C the ketone-de-

(13) Sharts, C. M.; Sheppard, W. A. *Org. React. (N.Y.)* **1974**, *21*, 137–154.

(14) The halogen fluorides ClF, BrF, and IF have been prepared under various conditions, including direct reaction of $F_2$ on the halogens $Cl_2$, $Br_2$ and $I_2$.[15,16] ClF, the only stable halogen monofluoride, has been isolated and characterized.[17] BrF and IF have been observed spectroscopically, but because they undergo rapid disproportionation, neither one has been isolated and fully characterized.[17] Although the reaction of N-halo compounds with HF is reported to generate the halogen fluorides in situ,[13] the materials produced by this method have not been characterized. However, their chemical behavior is analogous to that of the halogen fluorides, and for the purpose of this paper, they will be referred to as the halogen fluorides.

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(17) Stein, L. In *Halogen Chemistry*; Gutmann, V., Ed.; Academic: New York, 1967; Vol. I, pp 133–206 and references therein.

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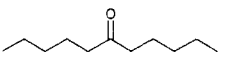
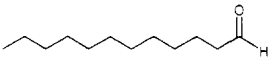
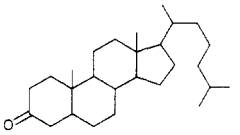
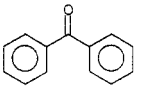
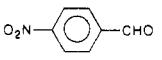
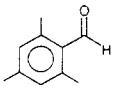
**Table I. Yield of Conversion of Ketones and Aldehydes 3 to 1,3-Dithiolanes 4 and *gem*-Difluoro Compounds 5**

| carbonyl | compound | yield (%)[a] 1,3-dithiolane (4) | yield (%)[a] *gem*-difluoro compound 5 | method[b] |
|---|---|---|---|---|
| 3a |  | 97 | 80 (90) | A |
| 3b |  | 80 | 86 | B |
| 3c |  | 70 | 75 (98) | A |
| 3d |  | 98 | 70 (90) | A |
| 3e |  | 95 | 61[c] (90) | A |
| 3f |  | 95 | 65 | B |
| 3g |  | 96 | 55 (70) | C |

[a] Yields refer to the isolated, purified compound. Yields in parentheses are determined by GLC with an internal standard. [b] Method A, 1 equiv of DBH, 20 equiv of $F^-$, −78 °C, 10 min; method B, 3 equiv of DBH, 20 equiv of $F^-$, 0 °C, 30 min; method C, 4 equiv of NIS, 20 equiv of $F^-$, −30 °C, 15 min. [c] Yield refers to chromatographically homogeneous crude product; purification by sublimation results in a significant loss of product.

rived dithiolane gave a good yield of the difluoro product **5a** after only 5 min; however, at warmer temperatures (ca. 25 °C), several byproducts are formed. Thus, the carbonium ions postulated as intermediates in the reaction sequence (Scheme I) appear to undergo side reactions at the higher temperature. Conversely, 2-undecyl-1,3-dithiolane (an aldehyde-derived dithiolane **4b**) required 5 min at 0 °C to provide a similar yield of the corresponding difluoro product **5b**. This is again consistent with the reaction sequence proposed in Scheme I, since one would expect that formation of carbocation E, with secondary substitution, would be slower than when it is tertiary.

In order to investigate reaction conditions that would be optimal, a series of reactions were run with dithiolane **4a** to examine the effect of different oxidants, reactant stoichiometry, and solvents. These reactions were analyzed by GLPC, using *n*-decane as an internal standard, and were repeated to obtain reliable and consistent results.

1,3-Dibromo-5,5-dimethylhydantoin (DBH) proved to be the most effective of several N-halo oxidants (Figure 1). After only 5 min, DBH provided a quantitative yield of **5a**, while *N*-iodosuccinimide (NIS) and *N*-bromosuccinimide (NBS) required 30 min to provide high yields. Although *N*-chlorosuccinimide (NCS) provided an 82% yield after only 5 min, longer reaction times led to formation of an unidentified product at the expense of product **5a**.

In the presence of a large excess of hydrogen fluoride–pyridine, we found that 1 mol of DBH was sufficient to effect complete conversion of 1 mol of dithiolane to the difluoro product (Figure 2). Since 1 mol of DBH provides 2 equiv of $Br^+$, this stoichiometry is consistent with the proposed mechanism (Scheme I).

The amount of hydrogen fluoride–pyridine used had a marked effect on the reaction time needed to achieve complete conversion. As shown in Figure 3, 20 equiv of fluoride produced a quantitative yield after only 5 min, whereas 60 min were required to achieve the same yield using only 6 equiv of fluoride. (Fluoride equivalents are based on the HF content (70%) of pyridinium poly(hydrogen fluoride).)

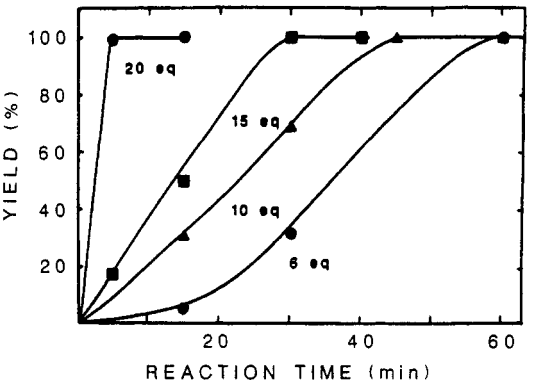


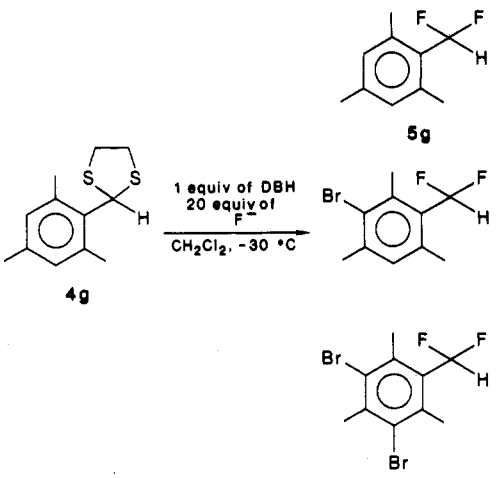

**Figure 3.** Time course of formation of 6,6-difluoroundecane (**5a**) from 2,2-dipentyl-1,3-dithiolane (**4a**) with various equivalents of fluoride. The dithiolane **4a** was treated with 1 equiv of DBH and fluoride (6–20 equiv) in $CH_2Cl_2$ at −78 °C. At the indicated times, an aliquot was removed, diluted with hexane, filtered through basic alumina, and analyzed by GLC. Quantitation was achieved by use of *n*-decane as an internal standard.

The reaction temperature limited solvent choices; however, $CH_2Cl_2$ worked well. As expected on the basis of the proposed carbocation intermediate (cf. Scheme I), hexane gave low yields of difluoro product even after 60 min. Although a 50% yield was obtained after 5 min in THF, longer reaction time led to the production of side products.

**Scope of the Reaction.** We have converted a variety of ketones (**3a,c–e**) and aldehydes (**3b,f**) into *gem*-difluoro compounds by this two-step method. The yields of dithiolane **4** and *gem*-difluoro product **5** are summarized in Table I.

The ketone-derived dithiolanes were fluorinated under the conditions optimized for 2,2-di-*n*-pentyl-1,3-dithiolane (**4a**). Initially, 1 molar equiv of DBH was dissolved in $CH_2Cl_2$ under nitrogen and cooled to −78 °C. Twenty equivalents of fluoride (in the form of hydrogen fluoride–

**Scheme II**




pyridine) were added, followed by the addition of the dithiolane. After 5 min, the product was isolated simply by adding an appropriate solvent (e.g., hexane) and passing the diluted reaction mixture through a short column of basic alumina. As shown in Table I, good yields of *gem*-difluoro compounds can be obtained from aliphatic, aromatic, steroidal, and cyclic aliphatic ketones.

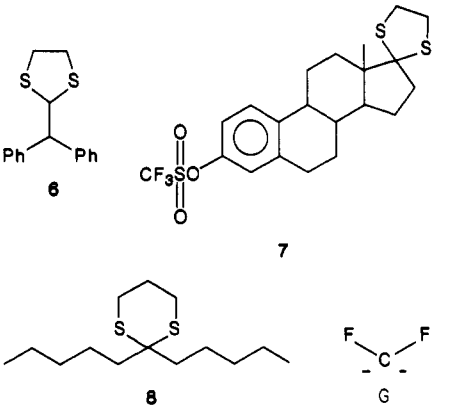
It is of particular note that ketone **3e** can be converted to the *gem*-difluoro compound **5e** by this method in 58% overall yield. The conversion utilizing sulfur tetrafluoride is reported to proceed in only 23% yield after 150 h in a pressure bomb at 30 °C; the yield is presumed to be low because transannular hydride shifts may be competing with fluorination at the higher reaction temperature.

As was mentioned earlier, aldehyde-derived dithiolanes require more vigorous conditions. Although rigorous optimization studies were not conducted, it was found that good yields of the corresponding 1,1-difluoro compounds were obtained after 30 min at 0 °C, with 3 molar equiv of DBH and 20 equiv of fluoride ion.

Although a variety of ketones and aldehydes can be efficiently fluorinated by this method, electron-rich aromatic systems will also give ring-brominated byproducts. As seen in Scheme II, when the dithiolane of mesitaldehyde (**4g**) was subjected to the fluorination conditions shown, the desired difluoro product **5g** was formed, along with the corresponding mono- and dibrominated species. However, these side products can be avoided by simply using *N*-iodosuccinimide (NIS) as the oxidant; the use of NIS provides only the difluoro compound **5g**.

It is essential in all these reactions to maintain strictly anhydrous conditions. If significant amounts of water are present, it competes with fluoride ion for reaction with the carbocation intermediates and leads to regeneration of the starting carbonyl compound. Also, the reaction fails to give clean products on systems susceptible to carbonium ion rearrangements. Thus, the dithiolanes of diphenylacetaldehyde (**6**) and estrone 3-trifluoromethane sulfonate (**7**) gave many products when subjected to the fluorination conditions.

Finally, in one case, the reactivity of a ketone-derived 1,3-dithiolane (**4a**) was compared to that of a 1,3-dithiane (**8**). When the corresponding derivatives of 6-undecanone were reacted with halogen fluoride under the same conditions (1 equiv, DBH; 20 equiv of $F^-$; −78 °C), the reaction of the dithiolane **4a** was much more rapid, giving a quantitative yield after only 5 min; the dithiane **8** produced an 80% yield only after 90 min. While slower and possibly less efficient, the successful fluorination of 1,3-dithianes is of particular significance, since anions of 1,3-dithianes




can be used in construction reactions.[22] Thus, by a combination of these reactions, the 1,3-dithiane system becomes the synthetic equivalent of a difluoromethyl 1,1-dianion (G).

## Conclusion

This new two-step fluorination procedure is an efficient method for transforming a ketone or aldehyde to the corresponding *gem*-difluoro compound and provides a simple, mild alternative to the use of sulfur tetrafluoride. The reactions are run in conventional laboratory glassware under atmospheric pressure and at low temperatures, and they proceed rapidly and in high yield.

## Experimental Section

**Caution.** Pyridinium poly(hydrogen fluoride), while more convenient to use than anhydrous hydrogen fluoride, requires similar safety precautions. It is extremely corrosive to human tissue, and contact with the skin, even in dilute concentrations, can result in painful, slow-healing burns which may not be visible for several hours.[23] This reagent should only be used in a well-ventilated hood with the user wearing protective clothing (lab coat, rubber gloves, etc.) and a full-face shield. Several treatments for hydrogen fluoride burns have been reported.[23]

**General Methods.** $^1H$ and $^{13}C$ NMR spectra were obtained at 200 MHz and 50.39 MHz, respectively, on a Varian XL 200 spectrometer and are reported in ppm downfield from $(CH_3)_4Si$ ($\delta$ scale). $^{19}F$ NMR spectra were obtained at 338.8 MHz on a Nicolet NT 360 spectrometer and are reported in ppm from $FCCl_3$ ($\phi^*$ scale). Melting points were taken on a Fischer-Johns melting point apparatus and are uncorrected. Mass spectra were obtained on a Varian MAT CH5 spectrometer at an ionization potential of 70 eV. High resolution mass spectra (HRMS) were obtained on a Varian MAT 731 spectrometer. Elemental analyses were performed by the Microanalytical Service Laboratory of the University of Illinois.

All reactions were monitored by analytical gas–liquid chromatography (GLC) on a Hewlett-Packard 5793A instrument equipped with a flame ionization detector. Analyses were performed on an Alltech RSL-150 capillary column (0.25 mm × 30 m). Preparative thin layer chromatography was performed on 2 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (particle size 0.032–0.063 mm) was used for flash chromatography.[24] Brinkmann basic $Al_2O_3$ (activity 1) was used for product isolation from the fluorination reactions. Glass columns should not be used for these procedures, since most reaction mixtures react exothermally with the evolution of gas when poured onto the alumina and will etch and possibly crack the glass. Fortuna[4] polypropylene/polyethylene syringes serve as convenient columns for reactions run on several millimole scale.

(22) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231–237.
(23) Trevino, M. A.; Herrman, G. H.; Sprout, W. L. *J. Occup. Med.* **1983**, *25*, 861–863.
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**General Procedure for the Synthesis of Dithiolanes from Aldehydes and Ketones. 2,2-Di-*n*-pentyl-1,3-dithiolane (4a).** 6-Undecanone (1.0 g, 5.87 mmol) and 0.99 mL (11.74 mmol) of 1,2-ethanedithiol were combined under nitrogen and stirred, followed by the addition of 0.82 mL (5.87 mmol) of $BF_3$·2HOAc. The biphasic solution was allowed to stir vigorously for 15 min. The mixture was diluted with hexane (20 mL) and washed with three 20-mL portions each of saturated $NaHCO_3$ solution, 15% NaOH solution, and brine. The organic extract was dried ($Na_2SO_4$) and concentrated. Purification by flash chromatography (5.0% diethyl ether/hexane) yielded 1.4 g (97%) of dithiolane **4a**: $^1H$ NMR ($CDCl_3$) $\delta$ 0.89 (t, 6 H), 1.33 (m, 12 H), 1.88 (t, 4 H), 3.27 (t, 4 H); mass spectrum, *m/z* (rel intensity) 246 (3, $M^+$), 175 (100), 105 (11), 73 (14), 61 (16), 55 (23), 41 (23). Anal. Calcd for $C_{13}H_{26}S_2$: C, 63.35; H, 10.63; S, 26.02. Found: C, 63.28; H, 10.78; S, 25.94.

**2,2-Diphenyl-1,3-dithiolane (4d).** Recrystallization from ethanol provided a 98% yield of dithiolane **4d** as a white crystalline solid: mp 105 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 3.41 (s, 4 H), 7.25 (m, 6 H), 7.60 (m, 4 H); mass spectrum, *m/z* (rel intensity) 258 (33, $M^+$), 233 (98), 229 (100), 198 (30), 165 (97), 121 (87), 77 (36). Anal. Calcd for $C_{15}H_{14}S_2$: C, 69.72; H, 5.46; S, 24.82. Found: C, 69.64; H, 5.51; S, 24.85.

**3-Cholestanone Ethylene Dithioketal (4c).** Recrystallization from ethanol provided a 70% yield of dithiolane **4c** as a white crystalline solid: mp 141–142 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 0.65 (s, 3 H), 0.83 (d, 6 H), 0.88 (s, 3 H), 0.895 (d, 3 H), 0.95–2.02 (br m, 31 H), 3.28 (t, 4 H); mass spectrum, *m/z* (rel intensity) 462 (65, $M^+$), 132 (28), 131 (26), 109 (27), 107 (30), 105 (29), 95 (47), 93 (35), 81 (100), 79 (26), 69 (35), 67 (30), 57 (47), 55 (49), 44 (41), 41 (34). Anal. Calcd for $C_{29}H_{50}S_2$: C, 75.26; H, 10.89; S, 13.85. Found: C, 75.29; H, 10.85; S, 13.86.

**Cyclododecanone Ethylene Dithioketal (4e).** Recrystallization from diethyl ether and pentane provided a 95% yield of dithiolane **4e** as clear, colorless platelets: mp 85–86 °C; spectral data is consistent with literature values.[25]

**2-Undecyl-1,3-dithiolane (4b).** Flash chromatography (2.0% diethyl ether/hexane) afforded an 80% yield of dithiolane **4b**: $^1H$ NMR ($CDCl_3$) $\delta$ 0.84 (t, 3 H), 1.22 (br s, 18 H), 1.77 (m, 2 H), 3.16 (m, 4 H), 4.43 (t, 1 H); mass spectrum, *m/z* (rel intensity) 260 (5, $M^+$), 105 (100), 61 (10), 55 (12), 43 (16), 41 (18). Anal. Calcd for $C_{14}H_{28}S_2$: C, 64.55; H, 10.83; S, 24.62. Found: C, 64.13; H, 10.90; S, 24.97.

**2-(*p*-Nitrophenyl)-1,3-dithiolane (4f).** Recrystallization from ethanol provided a 95% yield of dithiolane **4f** as a yellow crystalline solid: mp 78–79 °C (lit.[26] mp 67–69 °C); $^1H$ NMR ($CDCl_3$) $\delta$ 3.48 (m, 4 H), 5.65 (s, 1 H), 7.68 (dm, 2 H, $J$ = 8.8 Hz), 8.17 (dm, 2 H, $J$ = 8.8 Hz); mass spectrum, *m/z* (rel intensity) 227 (81, $M^+$), 199 (46), 182 (100), 166 (37), 152 (73), 121 (24), 77 (49), 60 (22), 45 (49). Anal. Calcd for $C_9H_9S_2NO_2$: C, 47.56; H, 3.99; S, 28.21; N, 6.16; O, 14.08. Found: C, 47.43; H, 4.17; S, 28.01; N, 6.09; O, 14.30.

**2-Mesityl-1,3-dithiolane (4g).** Recrystallization from ethanol provided a 96% yield of dithiolane **4g** as a white crystalline solid: mp 56–58 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 2.24 (s, 3 H), 2.54 (s, 6 H), 3.42 (m, 4 H), 6.28 (s, 1 H), 6.82 (s, 2 H); mass spectrum, *m/z* (rel intensity) 224 (9, $M^+$), 181 (15), 164 (12), 163 (100), 148 (15). Anal. Calcd for $C_{12}H_{16}S_2$: C, 64.23; H, 7.19, S, 28.58. Found: C, 63.88; H, 7.26; S, 28.86.

**2,2-Di-*n*-pentyl-1,3-dithiane (8).** 6-Undecanone (1.0 g, 5.87 mmol) and 1.18 mL (11.74 mmol) of 1,3-propanedithiol were combined under nitrogen and stirred, followed by the addition of 0.82 mL (5.87 mmol) of $BF_3$·2HOAc. The biphasic solution was allowed to stir vigorously for 30 min. The mixture was diluted with hexane (20 mL) and washed with three 20-mL portions each of saturated $NaHCO_3$ solution, 15% NaOH solution, and brine. The organic extract was dried ($Na_2SO_4$) and concentrated. Purification by flash chromatography (2.0% diethyl ether/hexane) yielded 1.37 g (90%) of dithiane 8: $^1H$ NMR ($CDCl_3$) $\delta$ 0.83 (t, 6 H), 1.30 (m, 12 H), 1.85 (m, 6 H), 2.73 (m, 4 H); mass spectrum, *m/z* (rel intensity) 260 (19, $M^+$), 189 (100), 97 (39), 74 (39), 55 (33), 41 (38). Anal. Calcd for $C_{14}H_{28}S_2$: C, 64.55; H, 10.83; S, 24.62. Found: C, 64.14; H, 10.87; S, 24.99.

**General Procedure for the Fluorination of Ketone-Derived Dithiolanes. 6,6-Difluoroundecane (5a).** 1,3-Dibromo-5,5-dimethylhydantoin (0.58 g, 2.03 mmol) was dissolved in 4.10 mL of dry $CH_2Cl_2$ and allowed to stir under nitrogen. The mixture was cooled to −78 °C and 1.00 mL (4.40 mmol, i.e., 40.6 equiv of $F^-$) of pyridinium poly(hydrogen fluoride) was added via polypropylene/polyethylene syringe, followed by the dropwise addition of dithiolane **4a** (0.50 g, 2.03 mmol). After 10 min, the reaction mixture, which was deep red, was diluted with hexane (30 mL) and filtered through a column (a 50-mL polypropylene/polyethylene syringe with a cotton plug) of basic alumina. Flash chromatography (2.0% diethyl ether/hexane) yielded 312 mg (80%) of difluoro compound **5a**: $^1H$ NMR ($CDCl_3$) $\delta$ 0.90 (t, 6 H), 1.26–1.50 (m, 12 H), 1.67–1.85 (m, 4 H); mass spectrum, *m/z* (rel intensity) 192 (5, $M^+$), 172 (40), 144 (23), 109 (41), 96 (72), 81 (100); $^{19}F$ NMR ($CDCl_3$) $\phi$* −98.14 ppm (quintet, $J$ = 16 Hz); $^{13}C$ NMR ($CDCl_3$) 125.4 (t, $J$ = 240 Hz, C-6), 36.3 (t, $J$ = 25.5 Hz, C-5, C-7), 31.6 (s, 2C), 22.4 (s, 2C), 22.0 (t, $J$ = 4.75 Hz, C-4, C-8), 13.8 (s, 2C). Anal. Calcd for $C_{11}H_{22}H_2$: C, 68.71; H, 11.53; F, 19.76. Found: C, 69.15; H, 11.36; F, 19.49.

**Difluorodiphenylmethane (5d).** Preparative TLC (5.0% diethyl ether/hexane) afforded a 70% yield of difluoro compound **5d**. The spectral data is consistent with literature values.[27]

**3,3-Difluorocholestane (5c).** Recrystallization from ethanol provided a 75% yield of difluoro compound **5c** as a white crystalline solid: mp 104–105 °C (lit.[5] mp 108–109 °C); $^1H$ NMR ($CDCl_3$) $\delta$ 0.65 (s, 3 H, 18-$CH_3$), 0.83 (d, $J$ = 5.08 Hz, 6 H, 26-,27-$CH_3$), 0.88 (s, 3 H, 19-$CH_3$), 0.895 (d, $J$ = 6.99 Hz, 3 H, 21-$CH_3$), 0.93–1.95 (br m, 31 H); mass spectrum, *m/z* (rel intensity) 408 (41, $M^+$), 254 (44), 253 (75), 81 (26), 57 (28), 55 (32), 43 (100), 42 (40), 41 (49); $^{19}F$ NMR ($CDCl_3$) $\phi$* −89.35 ppm (d, 3$\beta$-F, $J_{FF}$ = 233.6 Hz), −99.2 (dtt, 3$\alpha$-F, $J_{FF}$ = 233.6 Hz, $J_{HF}$ = 34.4, 13.2 Hz). Anal. Calcd for $C_{27}H_{46}F_2$: C, 79.35; H, 11.35; F, 9.30. Found: C, 78.98; H, 11.27; F, 9.25.

**Difluorocyclododecane (5e).** Evaporation of solvent afforded a 61% yield of chromatographically pure difluoro compound **5e**. Further purification for microanalytical analysis was performed by sublimation at 60 °C (18 mmHg) to provide the white crystalline solid: mp 43–45° C (lit.[28] mp 42–44 °C); $^1H$ NMR ($CDCl_3$) $\delta$ 1.33–1.50 (br m, 18 H), 1.90 (m, 4 H); mass spectrum, *m/z* (rel intensity) 121 (33), 100 (28), 96 (32), 95 (32), 83 (25), 82 (58), 81 (46), 69 (44), 68 (42), 67 (45), 56 (37), 55 (98), 54 (27), 44 (43), 43 (35) 41 (100); $^{19}F$ NMR ($CDCl_3$) $\phi$* −91.61 ppm (quintet, $J$ = 14.7 Hz). Anal. Calcd for $C_{12}H_{22}F_2$: C, 70.55; H, 10.85; F, 18.60. Found: C, 70.15; H, 10.99; F, 18.86.

**General Procedure for the Fluorination of Aldehyde-Derived Dithiolanes. Difluorododecane (5b).** 1,3-Dibromo-5,5-dimethylhydantoin (1.65 g, 5.76 mmol) was dissolved in 12 mL of dry $CH_2Cl_2$ and allowed to stir under nitrogen. The mixture was cooled to 0 °C and 0.95 mL (4.16 mmol i.e. 38.4 equiv of $F^-$) of pyridinium poly(hydrogen fluoride) was added via polypropylene/polyethylene syringe, followed by the dropwise addition of dithiolane **4b** (0.50 g, 1.92 mmol). After 30 min, the reaction mixture, which was deep red, was diluted with hexane (30 mL) and filtered through a column (a 50-mL polypropylene/polyethylene syringe with a cotton plug) of basic alumina. The organic solution was dried ($Na_2SO_4$), concentrated, and distilled to yield 341 mg (86%) difluoro compound **5b**: bp 55–57 °C (1.0 mmHg); $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (t, 3 H), 1.36 (m, 18 H), 1.78 (br m, 2 H), 5.79 (tt, 1 H, $J$ = 57 Hz); mass spectrum, *m/z* (rel intensity) 206 (3, $M^+$), 85 (19), 71 (35), 57 (92), 56 (17), 55 (28), 43 (100), 42 (16), 41 (52); $^{19}F$ NMR ($CDCl_3$) $\phi$* −116.22 ppm (dt, $J_{FF}$ = 57 Hz, $J_{HF}$ = 17.6 Hz); HRMS calcd for $C_{12}H_{24}F_2$ 206.1847, found 206.1847. Anal. Calcd for $C_{12}H_{24}F_2$: C, 69.86, H, 11.73; F, 18.41. Found: C, 70.03; H, 11.56; F, 18.41.

**4-(Difluoromethyl)nitrobenzene (5f).** Flash chromatography (20% ethyl acetate/hexane) afforded 65% of difluoro compound **5f**: $^1H$ NMR ($CDCl_3$) $\delta$ 6.75 (t, 1 H, $J$ = 55.6 Hz), 7.72 (d, 2 H, $J$ = 8.3 Hz), 8.33 (d, 2 H, $J$ = 8.3 Hz); mass spectrum, *m/z* (rel intensity) 173 (59, $M^+$), 127 (100), 107 (18), 101 (22), 77 (23), 51

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(15), 50 (17); $^{19}F$ NMR ($CDCl_3$) $\phi^*$ -113.45 ppm (doublet, $J$ = 51.4 Hz) (lit. value -71.5 ppm[29]); HRMS calcd for $C_7H_5F_2NO_2$ 173.0295, found 173.0291.

**General Procedure for the Fluorination of Electron-Rich Aromatic Systems Using *N*-Iodosuccinimide To Avoid Aromatic Ring Bromination. 1-(Difluoromethyl)-2,4,6-trimethylbenzene (5g).** *N*-Iodosuccinimide (2.01 g, 8.92 mmol) was dissolved in 18 mL of dry $CH_2Cl_2$ and allowed to stir under nitrogen. The mixture was cooled to -30 °C, and 1.10 mL (4.83 mmol, i.e., 44.6 equiv of $F^-$) of pyridinium poly(hydrogen fluoride) were added via polypropylene/polyethylene syringe, followed by the dropwise addition of dithiolane **4g** (0.50 g, 2.23 mmol) in 1.0 mL of $CH_2Cl_2$. After 15 min, the reaction mixture (which was dark purple) was diluted with $CH_2Cl_2$ (30 mL) and filtered through a column (a 50-mL polypropylene/polyethylene syringe with a cotton plug) of basic alumina. The organic solution was dried ($Na_2SO_4$) and concentrated. Preparative TLC (10% diethyl ether/hexane) afforded 55% of the difluoro compound **5g**: $^1H$ NMR ($CDCl_3$) $\delta$ 2.42 (s, 3 H), 2.43 (s, 6 H), 6.86 (s, 2 H), 6.94 (t, 1 H, $J$ = 54.4 Hz); mass spectrum, $m/z$ (rel intensity) 170 (47, $M^+$), 155 (21), 119 (100), 91 (23), 51 (33), 39 (29); $^{19}F$ NMR ($CDCl_3$) $\phi^*$ -111.78 ppm (doublet, $J$ = 54.1 Hz). Anal. Calcd for $C_{10}H_{12}F_2$: C, 70.57; H, 7.11; F, 22.32. Found: C, 70.87; H, 7.04; F, 22.10.

**General Procedure for the Fluorination of Ketone-Derived Dithianes. 6,6-Difluoroundecane (5a).** 1,3-Dibromo-5,5-dimethylhydantoin (1.65 g, 5.76 mmol) was dissolved in 12 mL of dry $CH_2Cl_2$ and allowed to stir under nitrogen. The mixture was cooled to -78 °C and 0.95 mL (4.16 mmol i.e., 38.4 equiv of $F^-$) of pyridinium poly(hydrogen fluoride) was added via polypropylene/polyethylene syringe, followed by the dropwise addition of dithiane **8** (0.50 g, 1.92 mmol). After 45 min, the reaction mixture was diluted with hexane (30 mL) and filtered through a column of basic alumina. Flash chromatography (2.0% diethyl ether/hexane) yielded 258 mg (70%) of difluoro compound **5a**.

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**Acknowledgment.** We are grateful for support of this research from the National Institutes of Health (PHS 5R01 CA 25836). High field NMR spectra were obtained on instruments in the NSF Regional Instrumentation Facility supported by a grant from the National Science Foundation (NSF CHE 79-16100) and high resolution mass spectrometry was performed on instruments supported by a grant from the National Institutes of Health (PHS GM 27029).

**Registry No.** **3a**, 927-49-1; **3b**, 112-54-9; **3c**, 15600-08-5; **3d**, 119-61-9; **3e**, 830-13-7; **3f**, 555-16-8; **3g**, 487-68-3; **4a**, 103383-69-3; **4b**, 103383-70-6; **4c**, 29575-88-0; **4d**, 6317-10-8; **4e**, 16775-67-0; **4f**, 41159-02-8; **4g**, 41159-04-0; **5a**, 103383-71-7; **5b**, 62127-45-1; **5c**, 16319-73-6; **5d**, 360-11-2; **5e**, 27415-48-1; **5f**, 29848-57-5; **5g**, 103383-72-8; **8**, 5849-09-2; 1,2-ethanedithiol, 540-63-6; 1,3-propanedithiol, 109-80-8; 1,3-dibromo-5,5-dimethylhydantoin, 77-48-5; pyridinium poly(hydrogen fluoride), 62778-11-4.

# Computer-Assisted Mechanistic Evaluation of Organic Reactions. 12. p$K_a$ Predictions for Organic Compounds in $Me_2SO$

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*Received March 4, 1986*

A new algorithm for p$K_a$ prediction has been implemented in the computer synthesis program CAMEO. This algorithm is based on a few organizing principles extracted from a large number of experimentally determined acidities in $Me_2SO$. It considers such molecular factors as field and electron-delocalization effects, hydrogen bonding, hybridization, and steric effects. Useful generalizations have also been developed for hetero–hetero activated systems, benzenoid compounds, and others. These organizing principles coupled with a small data base make it possible to predict the acidities of a vast number of organic compounds to within 2 p$K_a$ units.

## I. Introduction

An interactive computer program, CAMEO, which predicts the products of organic reactions given starting materials and conditions, is under continued development. A key aspect of the program is that it does not use large, internally stored data bases, but rather general organizing principles and algorithms. The recognition of such principles is fundamentally important in addition to permitting greater efficiency in the program. Mechanistic rules have been developed to handle base-catalyzed and nucleophilic chemistry[1] including some organometallic reactions,[2] organosilicon chemistry,[3] acid-catalyzed and electrophilic reactions,[4] nucleophilic[5] and electrophilic[6] aromatic substitution, and thermal pericyclic processing including cycloadditions and sigmatropic and electrocyclic rearrangements.[7,8]

A knowledge of p$K_a$ values for organic compounds is important to the program as well as to the chemist. It is essential to have this information in order to determine the feasibility of proton transfer. Since proton transfer is often the first step in a base-catalyzed reaction, prediction of reaction products would not be possible without knowledge of acidities. The continued development of the program has identified a need for a more generalized and comprehensive algorithm for p$K_a$ determination. The old version of the program used a data driven algorithm in which functional group numbers were stored in an array of acidity levels.[1,2] This array was then used following functional group perception to determine the most acidic hydrogens. Although the old algorithm covered a large number of compounds, various limitations such as the inability to handle triactivation and substituted aromatic compounds prompted the need for a change.

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