Notes

The Synthesis of *gem*-Bis(difluoramino) Ketones and Unsaturated Derivatives[1]

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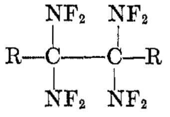
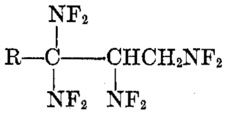
The synthesis of certain poly(difluoramino) structures such as **1** and **2** has not been possible using the known chemistry of tetrafluorohydrazine[3] and difluoramine.[4] While 1,4-diketones have been reported to give 1,1,4,4-tetrakis(difluoramino) derivatives with difluoramine in sulfuric acid,[4a] the synthesis of the tetrakis(difluoramino) adduct **1** from a 1,2-diketone under similar conditions has not been successful. In addition, the preparation of poly(difluoramino) derivatives, such as **2**, by combining the reactions of both the difluoramino reagents has been complicated by the fact that α,β-unsaturated carbonyl compounds undergo a Michael-type reaction with difluoramine.[4a] However, tetrafluorohydrazine and difluoramine have been successfully utilized in the synthesis of 1,2,2-tris(difluoramino)alkanes **3** from enol esters.[5]



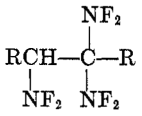
$R{-}C(NF_2)_2{-}C(NF_2)_2{-}R$

1



$R{-}C(NF_2)_2{-}CH(NF_2)CH_2NF_2$

2

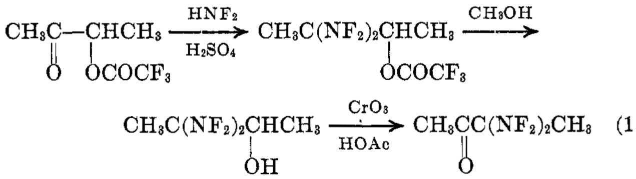


$RCH(NF_2){-}C(NF_2)_2{-}R$

3

Our approach to the synthesis of tetrakis(difluoramino) structures, such as **1** and **2**, involved the preparation of *gem*-bis(difluoramino) derivatives possessing the necessary functionality for further reaction with either tetrafluorohydrazine or difluoramine. We now describe the synthesis of several new classes of *gem*-bis(difluoramino) compounds: 3,3-bis(difluoramino)-2-butanone (**4**), 2,2-bis(difluoramino)cyclohexanone (**5**), 3,3-bis(difluoramino)-1-butene (**7**), and 3,3-bis(difluoramino)-1-butyne (**9**).

The reaction sequence employed for the preparation of the *gem*-bis(difluoramino) ketone derivatives **4** and **5** is illustrated below for compound **4** (eq 1). The use of the α-trifluoroacetoxy ketone in the initial reaction in this sequence was essential since the α-hydroxy ketone would easily undergo dehydration under the acidic conditions used and result in a completely different reaction. Both of the ketone products **4** and **5** obtained by this synthetic method were colorless liquids under atmospheric conditions. However, compound **4** was a volatile liquid and difficult to handle quantitatively. Solutions of 3,3-bis(difluoramino)-2-butanone in concentrated or dilute aqueous sulfuric acid resulted in decomposition of the ketone with the loss of difluoramine. Because of the instability of the *gem*-bis(difluoramino)keto structure in acidic media, the synthesis of the tetrakis(difluoramino) derivatives from ketones **4** and **5** was not possible.

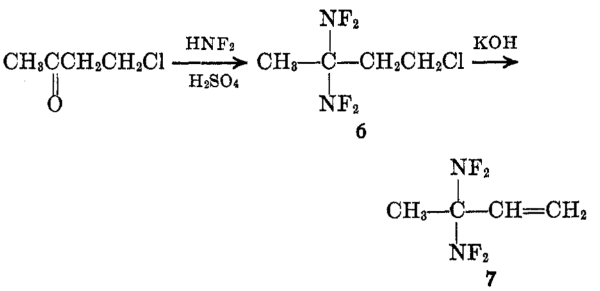


$$CH_3C(=O){-}CH(OCOCF_3)CH_3 \xrightarrow[H_2SO_4]{HNF_2} CH_3C(NF_2)_2CH(OCOCF_3)CH_3 \xrightarrow{CH_3OH}$$

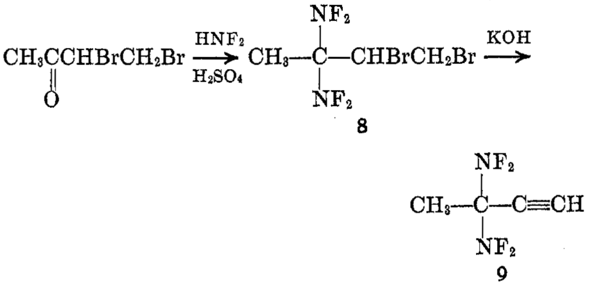
$$CH_3C(NF_2)_2CH(OH)CH_3 \xrightarrow[HOAc]{CrO_3} CH_3C(=O)C(NF_2)_2CH_3 \quad (1)$$

4

The preparation of the *gem*-bis(difluoramino) unsaturated derivatives **7** and **9** involved the reaction of halo ketones with difluoramine followed by dehydrohalogenation of the corresponding difluoramino adducts (see eq 2 and 3). The reaction of the halo ketones with difluoramine in sulfuric acid proceeded in a normal manner to give high yields of the corresponding difluoramino adducts **6** and **8**. Dehydrohalogenation of **6** and **8** to the *gem*-bis(difluoramino)-butene **6** and butyne **9** was accomplished in a vacuum system at room temperature using potassium hydroxide in triethylene glycol. The use of the high-boiling glycol solvent in these unusually facile reactions was necessary for convenient product isolation.



$$CH_3C(=O)CH_2CH_2Cl \xrightarrow[H_2SO_4]{HNF_2} \underset{\mathbf{6}}{CH_3{-}C(NF_2)_2{-}CH_2CH_2Cl} \xrightarrow{KOH} \underset{\mathbf{7}}{CH_3{-}C(NF_2)_2{-}CH{=}CH_2} \quad (2)$$



$$CH_3C(=O)CHBrCH_2Br \xrightarrow[H_2SO_4]{HNF_2} \underset{\mathbf{8}}{CH_3{-}C(NF_2)_2{-}CHBrCH_2Br} \xrightarrow{KOH} \underset{\mathbf{9}}{CH_3{-}C(NF_2)_2{-}C{\equiv}CH} \quad (3)$$

The effect of the strong electron-withdrawing property of the *gem*-bis(difluoramino) structure[4a,6] on the acidity of the α hydrogens is noted in the relatively mild conditions used for the dehydrohalogenation reactions. The stability of the *gem*-bis(difluoramino) compounds under the strongly basic conditions used for the dehydrohalogenation is entirely consistent with the known

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[3] R. C. Petry and J. P. Freeman, *J. Org. Chem.*, **32**, 4034 (1967).

[4] (a) K. Baum, *J. Amer. Chem. Soc.*, **90**, 7083 (1968); (b) K. Baum, *ibid.*, **90**, 7089 (1968).

[5] J. P. Freeman, R. C. Petry, and T. E. Stevens, *ibid.*, **91**, 4778 (1969).

[6] R. Ettinger, *J. Phys. Chem.*, **67**, 1558 (1963).

inertness of this difluoramino structure toward base.[7] Both primary and secondary alkyldifluoramines are readily dehydrofluorinated in basic media.[3]

Several attempts were made to add tetrafluorohydrazine to the 1-butene **7** under various conditions without success. Most of the reactions were done at elevated temperatures and resulted in the decomposition of **7**. Reaction of 1-butyne **9** with difluoramine in concentrated sulfuric acid did not give the tetrakis(difluoramino) derivative nor was it possible to effect the hydration of **9** to the ketone **4** using mercuric salts. Acetylene hydration has been established as an intermediate step in the formation of *gem*-bis(difluoramino)alkanes from dialkylacetylenes and difluoramine in sulfuric acid.[4b]

Experimental Section

Caution! Difluoramine and tetrafluoramine are explosive and should be handled with extreme care; see ref 3 and 8 for precautions.

Infrared spectra were obtained with a Perkin-Elmer Model 137B Infracord. The nmr spectra were obtained in tetramethylsilane–Freon 11 (CCl_3F) solution (used as references) using Varian Associates Model A-60 and HR-60 spectrometers. Both 4-chloro-2-butanone[9] and 3,4-dibromo-2-butanone[10] were prepared as described in the literature. 3-Trifluoroacetoxy-2-butanone [$n^{22}D$ 1.3568, bp 87–90° (131 mm)] was prepared from 3-bromo-2-butanone and silver trifluoroacetate. 2,2-Bis(difluoramino)-3-trifluoroacetoxybutane was prepared from the corresponding ketone and difluoramine. Alcohol exchange of the former with methanol gave 3,3-bis(difluoramino)-2-butanol. The three compounds in this reaction sequence as well as the analogous cyclohexyl derivatives (prepared similarly) were isolated, purified, and fully characterized.

3,3-Bis(difluoramino)-2-butanone (4).—A solution of 0.099 g (0.09 mmol) of chromium trioxide in 1 ml of glacial acetic acid was degassed using a liquid nitrogen cooling bath and then charged with 0.173 g (0.9 mmol) of 3,3-bis(difluoramino)-2-butanol *via* a vacuum bulb-to-bulb transfer. The reaction mixture was stirred under a static vacuum at room temperature for 3 hr. The entire liquid contents of the reactor were separated from chromium salts by a vacuum bulb-to-bulb transfer. The colorless liquid was then treated with small portions of solid sodium carbonate until the evolution of carbon dioxide ceased. A final distillation of the residual liquid from the sodium acetate gave the volatile liquid ketone (**4**): 0.087 g (50%); ν_{gas} 1723 (C=O), 970 and 925 cm^1 (NF); H^1 nmr τ 8.22 (quintet, $CH_3C(NF_2)_2$), 7.6 (s, CH_3-C=O); ^{19}F nmr Φ -31.7 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_6F_4N_2O$: C, 27.58; N, 16.09; F, 43.66. Found· C, 27.3; N, 14.7; F, 42.6.

2,2-Bis(difluoramino)cyclohexanone (5).—The oxidation of 2,2-bis(difluoramino)cyclohexanol with chromium trioxide in glacial acetic acid was done in a manner similar to that described above for the preparation of **4**. The cyclohexanone **5** was obtained in 39% yield as a colorless liquid: ν_{neat} 1723 (C=O),1010, 980, 910, and 900 cm^{-1} (NF); ^{19}F nmr Φ -27.6 ($C(NF_2)_2$).

Anal. Calcd for $C_6H_8F_4N_2O$: C, 36.0; N, 14.0; F, 37.97. Found: C, 36.6; N, 13.4; F, 38.3.

3,3-Bis(difluoramino)-1-chlorobutane (6).—Sulfuric acid (2 ml, 100%) in a 20-ml glass pressure reactor[11] was degassed using a liquid nitrogen cooling bath, and 0.8 g (0.0075 mol) of 4-chloro-2-butanone was added to the frozen acid by vacuum transfer. The mixture was then charged with 2.5 g (0.047 mol) of difluoramine at $-128°$ (Freon 21–liquid nitrogen bath). The reaction mixture was allowed to warm to 25° and stirred at ambient temperature for 2 hr. Removal of the excess difluoramine and vacuum transfer gave product **6**: 1.07 g (74%); ν_{neat} 1000, 900, 910, and 885 cm^{-1} (NF), 740 (CCl); ^1H nmr τ 7.46 and 6.31 (2 doublets, $J_{HH} = 8.0$ Hz), 8.34 (quintet, $J_{HF} = 2.0$ Hz); ^{19}F nmr Φ -27.5 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_7ClF_4N_2$: C, 24.69; N, 14.39. Found: C, 24.89; N, 15.54.

3,3-Bis(difluoramino)-1-butene (7).—A solution of 0.618 g (0.0032 mol) of **6** in 2 ml of a potassium hydroxide–triethylene glycol solution[13] was stirred for 2.5 hr at 25° under static vacuum. Vacuum bulb-to-bulb transfer gave the volatile liquid product **7**: 0.45 g (90%); ν_{neat} 3110 ($C=CH_2$), 990, 980, 955, 900, and 880 cm^1 (NF). The ^1H nmr spectrum consisted of a quintet at τ 8.29 ($J_{HF} = 2.0$ Hz) and an ABC pattern for the vinyl protons centered at τ 3.80, 4.25, and 4.32 ($J_{AB} = 8.0$ Hz, $J_{BC} = 20$ Hz, $J_{AC} = 19$ Hz). The ^{19}F nmr spectrum had one signal at Φ -28.9 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_6F_4N_2$: C, 30.38; N, 17.72; F, 48.07. Found: C, 30.34; N, 17.55; F, 47.0.

3,3-Bis(difluoramino)-1,2-dibromobutane (8).—This compound was prepared in 91% yield from 3,4-dibromo-2-butanone and difluoramine in 100% sulfuric acid using a procedure similar to that described for compound **6**. The infrared spectrum of **8** showed the characteristic -NF frequencies at 1000, 980, 910, and 895 cm^{-1}. The ^1H nmr of **8** exhibited signals at τ 8.22 (CH_3), 6.48 (-CHBr), and 5.61 (CH_2Br) and the ^{19}F nmr spectrum had one signal at Φ -29.2 ($C(NF_2)_2$).

Anal. Calcd for $C_4H_6Br_2F_4N_2$: C, 15.11; H, 1.88; N, 8.80. Found: C, 15.32; H, 1.67; N, 8.61.

3,3-Bis(difluoramino)-1-butyne (9).—A solution of 1.01 g (0.0032 mol) of **8** in 3 ml of a potassium hydroxide–triethylene glycol solution[13] was stirred for 5 hr at 25° under static vacuum. Vacuum bulb-to-bulb transfer provided 0.50 g of a liquid condensate at $-128°$. However, upon warming to 25°, the liquid vaporized to a gas. This gaseous product was established as a 6:1 mixture of the 1-butyne (**9**) and 3,3-bis(difluoramino)-2-bromo-1-butene,[14] respectively, by vpc analysis on a 2-m 30% DC-200 on a Chromosorb column. The assignment of the 1-butyne structure **9** to the major component of this mixture was based upon the following data: ν_{gas} 3320 and 2120 ($C\equiv CH$), 990, 910, and 895 cm^{-1} (NF); ^1H nmr τ 8.13 ($C\equiv CH$); ^{19}F nmr Φ -32.1 and -37.3 (AB system, $\Delta_{FF} = 5.2$ ppm and $J_{FF} = 615$ Hz).

Registry No.—**4**, 27723-17-7; **5**, 27723-18-8; **6**, 24426-01-5; **7**, 27723-20-2; **8**, 27723-21-3; **9**, 27723-22-4.

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[7] K. Baum, *J. Org. Chem.*, **34**, 3377 (1969).

[8] J. P. Freeman, A. Kennedy, and C. B. Colburn, *J. Amer. Chem. Soc.*, **82**, 5304 (1960).

[9] L. I. Smith and J. A. Sprung, *ibid.*, **65**, 1276 (1943).

[10] E. R. Buchman and H. Sargent, *ibid.*, **67**, 400 (1945).

[11] This reactor has been previously described[12] and was purchased from Scientific Glass Apparatus Co., Bloomfield, N. J.

[12] R. P. Rhodes, *J. Chem. Educ.*, **40**, 423 (1963).

[13] This solution was prepared by stirring a mixture of 2.8 g of potassium hydroxide in 10 ml of triethylene glycol at room temperature for 1 hr and decanting the supernatant liquid for use in the reaction.

[14] This compound was isolated by preparative vpc and its structure established by nmr analysis.

The Synthesis of β-Hydroxy Acids Using α-Lithiated Carboxylic Acid Salts

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The recent publications by Creger[2] have reported the α lithiation of aliphatic carboxylic acids using lithium diisopropylamide in tetrahydrofuran. The α-lithiated acid salts thus formed have been shown to react with alkyl halides and with epoxides.

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[2] P. L. Creger, *J. Amer. Chem. Soc.*, **89**, 2500 (1967); *ibid.*, **92**, 1396, 1397 (1970).