NUCLEOPHILIC SUBSTITUTION REACTIONS OF POLYFLUOROALKYLSULFONAMIDES

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SUMMARY

The sulfonamides $CF_3SO_2N(CH_3)Na$ and $CF_3SO_2N(H)Na$ have been reacted with polyfluoro cyclic, acyclic and inorganic chlorine and bromine-containing species. Nucleophilic displacement of chlorine or bromine in 1,2-dichloroperfluorocyclobutene, 1,2-dichloroperfluorocyclopentene, benzyl bromide, cyanuric chloride and oxalyl chloride has been found to occur under mild conditions to give good yields of N-substituted polyfluoroalkyl and polyfluoroaryl sulfonamides. The effects of solvent and substrate structure on the conditions necessary for reaction to occur, and the yields obtained of the desired products are discussed.

INTRODUCTION

Reactions of fluorocarbons with a variety of nucleophiles have been an area of intense study over the last forty years. An excellent discussion on the behavior of fluorocarbons with nucleophiles appears in the older literature [1]. Much of the work reported involves reactions of alcohols or alkoxides [2],[3],[4],[5],[6], single electron transfer catalysis of alkoxide reactions [7], the generation of radical anions from perfluoroalkylsulfonyl iodides [8], or perfluoroalkyl iodides [9], nitrogen-containing nucleophiles (other than sulfonamide) [10], and nucleophiles generated from per- and polyfluoroalkenes in the presence of fluoride ion [11],[12],[13]. Far less numerous are reports on the synthesis and reaction chemistry of polyfluoroalkylsulfonamides [14],[15],[16]. In addition, these strong nucleophiles have not ordinarily been included in general discussions of fluorinated nucleophiles and their reactivity with respect to displacement of halogen (chlorine or

0022-1139/91/$3.50

bromine) from polyfluorocarbons. In this paper we describe facile methods for the preparation of several new mono- and bifunctional polyfluorosulfonamides via the displacement of chlorine or bromine through nucleophilic reactions of sulfonamide anions. In addition, we compare the relative reactivity of two nucleophiles ($CF_3SO_2N(CH_3)Na$ and $CF_3SO_2N(H)Na$), and the effect that different aprotic solvents (dimethylformamide, acetonitrile, dimethylsulfoxide and tetrahydrofuran) exhibits on reaction conditions and yields of the desired products.

RESULTS AND DISCUSSION

Sulfonamides and sulfamides, both heterocyclic and acyclic derivatives, are important classes of compounds in a large number of areas. Many are useful biologically active materials [17], while others find application in areas as diverse as textiles [18], photography [19], electrodeposition processes [20], and herbicides [21]. Most of these materials are nonfluorinated, or contain a single fluorine or trifluoromethyl group. An excellent review of their syntheses and chemistry has been published recently [17].

It is well known that reactions of functionalized hydrocarbons and fluorocarbons differ markedly. For example, in contrast to hydrocarbon olefins, fluorocarbon olefins are typically unreactive towards electrophiles, and readily undergo nucleophilic addition. For low molecular weight olefins, addition of Nu-X is predominant, while substitution and the formation of unsaturated products is normally observed for branched, cyclic or internal polyfluoro olefins. Furthermore, perfluoroalkyl halides (R_fX; X = Cl, Br, I) are generally unreactive towards nucleophilic substitution, while hydrocarbon halides react readily. The polyfluorinated systems we have studied in reactions with fluorinated sulfonamides provide no exceptions to these general observations.

The cyclic alkenes, 1,2-dichloroperfluorocyclobutene and 1,2-dichloroperfluorocyclopentene, react under mild conditions to give disubstituted products.

$$CF_3SO_2N(CH_3)Na + ClC{=}C(Cl)(CF_2)_nCF_2 \xrightarrow[36h]{RT} CF_3SO_2N(CH_3)C{=}C[N(CH_3)SO_2CF_3](CF_2)_nC \quad n = 1,2$$

In no case, even in the presence of a large excess of the 1,2-dichloro-

cycloalkene, was a singly substituted product obtained. It is somewhat surprising that no reaction takes place with 1,2-dichloroperfluorocyclohexene, even after two days at 60 °C. However, this result is consistent with previous reports describing the chemistry of this compound [22].

Cyanuric chloride readily forms the trisubstituted sulfonamide $[NCN(CH_3)SO_2CF_3]_3$ when reacted with $CF_3SO_2N(CH_3)Na$ for eight hours at room temperature. Oxalyl chloride proves to be even more labile, and $[CF_3SO_2N(CH_3)C(O)]_2$ is formed in good yield after eight hours at 0 °C.

While pentafluorobenzylbromide reacts with $CF_3SO_2N(CH_3)Na$ to give the N-substituted sulfonamide $CF_3SO_2N(CH_3)CH_2C_6F_5$, with $CF_3SO_2N(H)Na$ the only sulfonamide product observed is $CF_3SO_2N(CH_2C_6F_5)_2$. The reaction is believed to proceed through the intermediate $CF_3SO_2N(H)CH_2C_6F_5$, however, this compound could not be isolated even when a large excess of sulfonamide was added.

In all cases, aprotic solvents were used. However, changes in the polarity of the solvent affected the reaction conditions necessary for product formation as well as the yields observed. In Table I, the data obtained for four-, five- and six-membered rings reacting with $CF_3SO_2N(CH_3)Na$ in dimethylformamide, acetonitrile, dimethylsulfoxide, and tetrahydrofuran are summarized.

TABLE I

Solvent and ring size effect on nucleophilic substitution with $CF_3SO_2N(CH_3)Na$

Solvent	Ring	Conditions	Product Yield (%)
Dimethylformamide	1,2-dichloroperfluorocyclobutene	RT, 8 h	80
	1,2-dichloroperfluorocyclopentene	50 °C, 10 h	65
	1,2-dichloroperfluorocyclohexene	60 °C, 48 h	No reaction
Acetonitrile	1,2-dichloroperfluorocyclobutene	50 °C, 48 h	55
Dimethylsulfoxide	1,2-dichloroperfluorocyclobutene	60 °C, 48 h	40
Tetrahydrofuran	1,2-dichloroperfluorocyclobutene	60 °C, 48 h	No reaction

In addition to reduced product formation with increasing ring size, not unexpectedly it is apparent that more polar solvents enhance the yield of the desired substitution products.

In conclusion, we have developed optimized methods for the synthesis of a variety of new mono- and bifunctional polyfluorosulfonamides. These routes should be amenable to the synthesis of a large number of such compounds from various polyfluorinated cyclic and acyclic substrates. In general, single products, which are easily isolated and purified, are obtained.

EXPERIMENTAL

The compounds $CF_3SO_2NH_2$, CF_3SO_2NHNa, and $CF_3SO_2N(CH_3)H$ were prepared by utilizing the literature methods [14],[15],[16]. The reagents 1,2-dichloroperfluorocyclobutene, 1,2-dichloroperfluorocyclopentene, 1,2-dichloroperfluorocyclohexene (PCR), and pentafluorobenzyl bromide (Aldrich) were purchased and used as received. Standard vacuum line techniques were used for the quantitation of all volatile materials. A JEOL FX-90Q and an IBM NR-300 FT NMR spectrometers were used to obtain ^{19}F and ^{1}H NMR spectra with CCl_3F and $(CH_3)_4Si$, respectively, as reference compounds. Infrared and mass spectral data were collected with a Perkin-Elmer Model 1710 FTIR equipped with an IBM PS-2 data station, and a VG 7070-HS GC/MS mass spectrometer operating in the CI mode, respectively.

Preparation of $CF_3SO_2N(CH_3)Na$

This compound was prepared by treating 10 mmol of $CF_3SO_2N(CH_3)H$ [16] with 12 mmol of sodium in ether at -20 °C. The sodium salt was obtained in approximately quantitative yield. After filtration, and washing with ether, it was dried for 24 h at 80 °C under vacuum prior to use. This hygroscopic white solid exhibited a singlet ^{19}F resonance at $\emptyset$ -80.26 and a singlet ^{1}H resonance at δ 3.62.

Preparation of $CF_3SO_2N(CH_3)\overline{C=C[N(CH_3)SO_2CF_3]CF_2CF_2}$

Into a 25 mL round-bottomed flask containing a solution of $CF_3SO_2N(CH_3)Na$ (0.50 g, 2.70 mmol) in 6 mL of DMF, was added 0.26 g (1.33

mmol) of 1,2-dichloroperfluorocyclobutene. The contents of the flask were stirred vigorously for 24 h, during which time sodium chloride precipitated slowly. The oil layer formed on the addition of 6 mL of water was separated and passed through a 30 cm by 0.5 cm glass column containing 200 mesh Al_2O_3. The eluate was dried under vacuum at room temperature to give 0.47 g (80% yield) of the title compound as a colorless, slightly viscous liquid. Spectral data obtained are: IR (thin film): 1682 s (C=C), 1418 vs (SO_2) cm^{-1}; NMR ^{19}F Ø -75.2 (CF_3, s), -133.9 (CF_2, s); NMR ^1H δ 3.68 (CH_3, s); CI MS [m/e (species) intensity]: 448 (M^+) 5, 429 (M^+ - F) 22, 316 (M^+ + 1 - CF_3SO_2) 100, 315 (M^+ - CF_3SO_2) 35, 182 (M^+ - 2(CF_3SO_2)) 30, 100 ($C_2F_4^+$) 12. Anal. Calcd. for $C_8F_{10}H_6N_2O_4S_2$: C, 21.41; F, 42.4; H, 1.34. Found: C, 21.67; F, 42.8; H, 1.39.

Preparation of $CF_3SO_2N(CH_3)\overline{C=C[N(CH_3)SO_2CF_3]CF_2^ACF_2^BCF_2}^A$

The compound 1,2-dichloroperfluorocyclopentene (0.66 g, 2.69 mmol) was added to a 25 mL round-bottomed flask containing a solution of $CF_3SO_2N(CH_3)Na$ (1.0 g, 5.40 mmol) in 10 mL of DMF. After stirring for 36 h at room temperature, the resulting mixture was poured into 15 mL of water. The oil layer was separated, passed through an Al_2O_3 column, and the solvent was removed under vacuum. The desired product was obtained in 60% yield as a colorless, viscous liquid. Spectral data obtained are: IR (thin film): 1680 m (C=C), 1420 s (SO_2) cm^{-1}; NMR ^{19}F Ø -79.34 (CF_3, s), -118.12 (CF_2^A, s), -138.36 (CF_2^B, s); NMR ^1H δ 3.40 (CH_3, s); CI MS [m/e (species) intensity]: 498 (M^+) 8.9, 479 (M^+ - F) 12.2, 366 (M^+ + 1 - CF_3SO_2) 100, 365 (M^+ - CF_3SO_2) 49.9, 260 (M^+ - $C_3F_7SO_2H_5$) 43.1, 231 (M^+ - 1 - 2(CF_3SO_2)) 28.7, 69 (CF_3^+) 44. Anal. Calcd. for $C_9F_{12}H_6N_2O_4S_2$: C, 21.68; F, 45.78; H, 1.21. Found: C, 21.71; F, 46.8; H, 1.47.

Preparation of $C_6F_5CH_2N(CH_3)SO_2CF_3$

A solution containing 0.22 g (1.19 mmol) of $CF_3SO_2N(CH_3)Na$ and 0.25 g (0.96 mmol) of $C_6F_5CH_2Br$ in 6 mL of DMSO was stirred vigorously at 60 °C for 12 h. After filtering to remove sodium bromide, the reaction mixture was combined with 6 mL of water. An oily layer consisting of the crude product was separated, and pure product was obtained by vacuum sublimation in 72%

yield as a white solid melting at 63 °C. Spectral data obtained are: NMR ^{19}F ϕ -74.56 (CF_3, s), -140.88 (2F, m), -151.21 (1F, m), -160.37 (2F, m); NMR ^1H δ 3.01 (CH_3, s); MS CI [m/e (species) intensity]: 344 ($M^+ + 1$) 3.2, 343 (M^+) 4.9, 274 ($M^+ - CF_3$) 5, 210 ($M^+ - CF_3SO_2$) 7.2, 209 ($M^+ - 1 - CF_3SO_2$) 30.4, 181 ($C_6F_5CH_2^+$) 65.8, 176 ($CF_3SO_2N(CH_3)CH_2^+$) 100, 69 (CF_3^+) 5. Anal. Calcd. for $C_9F_8H_5NO_2S$: C, 31.49; F, 44.3; H, 1.46. Found: C, 31.34; F, 44.1; H, 1.44.

Preparation of $CF_3SO_2N(CH_2C_6F_5)_2$

Solutions of $CF_3SO_2N(H)Na$ (0.36 g, 2.1 mmol) in 7 mL of DMF, and $C_6F_5CH_2Br$ (0.4 g, 1.5 mmol) in 3 mL of DMF, were combined and stirred at 85 °C for 24 h. Water was then added to the reaction mixture, and the crude product (a yellow oil) was extracted with ether. Further purification by liquid chromatography (using a solvent mixture composed of 4 parts of petroleum ether and 1 part of chloroform on a 30 cm by 0.5 cm Al_2O_3 column) resulted in the isolation of a 30% yield of the desired product, a white solid which melts at 76-77 °C. Spectral data obtained are: NMR ^{19}F ϕ -76.15 (CF_3, s), -142.95 (4F, m), -157.57 (2F, m), -164.01 (4F, m); NMR ^1H δ 4.76 (CH_3, s); MS CI [m/e (species) intensity]: 509 (M^+) 2.8, 376 ($M^+ - CF_3SO_2$) 9, 342 ($M^+ - C_6F_5$) 31.2, 181 ($C_6F_5CH_2^+$) 100, 167 ($C_6F_5^+$) 17, 149 ($C_6F_4H^+$) 36.8, 69 (CF_3^+) 9. Anal. Calcd. for $C_{15}F_{13}H_4NO_2S$: C, 35.36; F, 48.53; H, 0.79. Found: C, 35.42; F, 48.7; H, 0.87.

Preparation of $(CF_3SO_2N(CH_3)CN)_3$

To cyanuric chloride (0.08 g, 0.43 mmol) dissolved in 5 mL of acetonitrile, a 0.25 g (1.35 mmol) acetonitrile solution of $CF_3SO_2N(CH_3)Na$ was added dropwise with stirring. The mixture was stirred at room temperature for 8 h, and the resulting white solid was separated by filtration, washed with water and dried under vacuum. A 56% yield (0.14 g) of the desired product (MP 205 °C) was obtained as a white solid. Spectral data obtained are: IR (thin film): 1410 (SO_2) cm^{-1}; NMR ^{19}F ϕ -73.43 s; NMR ^1H δ 3.31 s; MS CI [m/e (species) intensity]: 566 ($M^+ + 2$) 12, 565 ($M^+ + 1$) 100, 433 ($M^+ + 2 - CF_3SO_2$) 26, 432 ($M^+ + 1 - CF_3SO_2$) 18, 431 ($M^+ - CF_3SO_2$) 93, 299 ($M^+ + 1 - 2(CF_3SO_2)$) 16.7, 165 ($M^+ - 3(CF_3SO_2)$) 48.5, 69 (CF_3^+) 35. Anal. Calcd. for $C_9F_9H_9N_6O_6S_3$: C, 19.5; F, 30.32; H, 1.60. Found: C, 19.4; F, 30.2; H, 1.7.

Preparation of $[CF_3SO_2N(CH_3)C(O)]_2$

Oxalyl chloride (0.07 g, 0.56 mmol) in acetonitrile (3 mL) was added dropwise at 0 °C with stirring to a 5 mL acetonitrile solution of 0.25 g (1.35 mmol) of $CF_3SO_2N(CH_3)Na$. The mixture was warmed rapidly to room temperature and stirred for an additional 8 h. Following the addition of 5 mL of water, the white solid formed was isolated by filtration, and purified by column chromatography on Al_2O_3 with petroleum ether/chloroform (4/1) as mobile phase. A 70% yield (0.15 g) of the product was isolated as a white solid (MP 90 °C). Spectral data obtained are: IR (KBr pellet): 1745 m, 1729 m (CO), 1412 s (SO_2) cm^{-1}; NMR ^{19}F ϕ 74.56 s; NMR ^1H δ 3.34 m; MS CI [m/e (species) intensity]: 380 (M^+) 14, 231 ($CF_3SO_2N(CH_2)C_2O_2N^+$) 23, 191 ($CF_3SO_2N(CH_3)CO^+ + 1$) 63; 190 ($CF_3SO_2N(CH_3)CO^+$) 100, 126 ($C_2F_2SO_2^+$) 100, 69 (CF_3^+) 100, 65 (HSO_2^+) 35. Anal. Calcd. for $C_6F_6H_4N_2O_6S_2$: C, 19.04; F, 30.2; N, 7.4. Found: C, 19.18; F, 30.5; N, 7.45.

ACKNOWLEDGEMENT

The authors would like to thank the National Science Foundation (Grant CHE-8703790) and the United States Air Force Office of Scientific Research (Grant 87-0067) for support of this work. We are also grateful to Dr. Gary Knerr for obtaining mass spectral data.

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