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Building up the Trifluoromethyl Group: A New Synthesis of α-Trifluoromethylketones.

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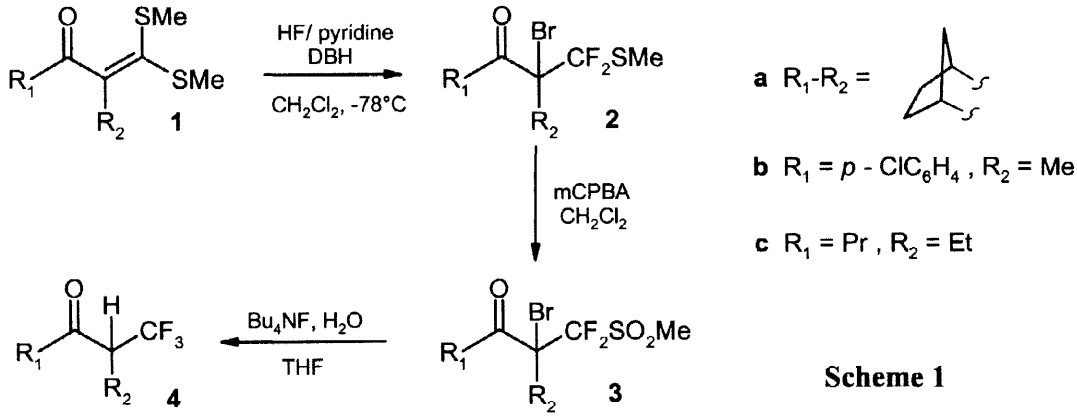
Abstract : α-Trifluoromethylketones were prepared from ketene dithioacetals derived from ketones, in a three step reaction involving only hydrogen fluoride and the fluoride anion as fluorinating agents.

The benefit of introducing the trifluoromethyl group into organic molecules, especially in the area of drugs or pesticides, is now well documented[1]. In the recent past, numerous new methods have been devised for this purpose[2]; most of them were based however on the use of fluorinated halocarbon (Halon) as starting materials. For example, α-trifluoromethylketones were prepared by condensation of trifluoromethyl bromide or of the expensive trifluoromethyl iodide with enamines[3,4] or silyl enol ethers[5]. Electrophilic trifluoromethylation of enolates[6] with trifluorinated sulfonium salts was also used for this purpose; this last reagent (Umemoto's reagent) being itself obtained starting from trifluoromethyl bromide. The ban on Halons and Freons, which are thought to be responsible for the phenomenon of ozone depletion in the stratosphere[7], gave an incentive for the quest of new fluorination reactions not making use of such class of reagents.

The replacement of sulfur functionality by a fluorine atom under oxidative conditions is a long known reaction[8]. Although numerous studies have been done in this area, to our knowledge only three publications were devoted to the elaboration of the carbon bonded trifluoromethyl group[9]. The first two references dealing with aromatics and the last one with alkenyl substrates. Thus, the introduction of a trifluoromethyl group on an aliphatic chain by this methodology remained unexplored.

A very interesting study by Bohlmann[10] on the fluorination of steroidal keto sulfides, as well as a remark on the mechanism of (unexpected ?) formation of a dibrominated product in a report by Hiyama[9c], led us to consider ketene dithioacetals[11] **1** as promising substrates for our purpose.



Scheme 1

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The strategy used for our synthesis is outlined in **scheme 1**. It consists of a stepwise introduction of the three fluorine atoms necessary to build up the trifluoromethyl group. The results are summarised in **table 1**.

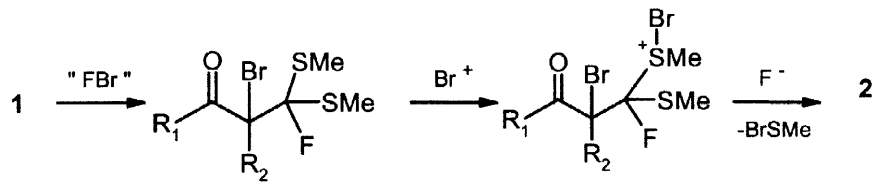
Table 1

Substrate	2 (Yield[a] from 1)	3 (Yield[a] from 2)	4 (Yield[a] from 3)
1a	**2a**[b] (65 %)	**3a**[b] (90 %)	**4a**[c] (70 %)
1b	**2b** (57 %)	**3b** (86 %)	**4b** (80 %)
1c	**2c** (39 %)	**3c** (92 %)	**4c** (42 %)

a) Isolated yields of analytically pure compounds. Spectral data are consistent with the assigned structures (see experimental for relevant data for entry **b**). b) 80 : 20 mixture of diastereoisomers. c) 60 : 40 mixture of diastereoisomers. This ratio is independent of the diastereoisomeric ratio of the starting sulfone **3a**.

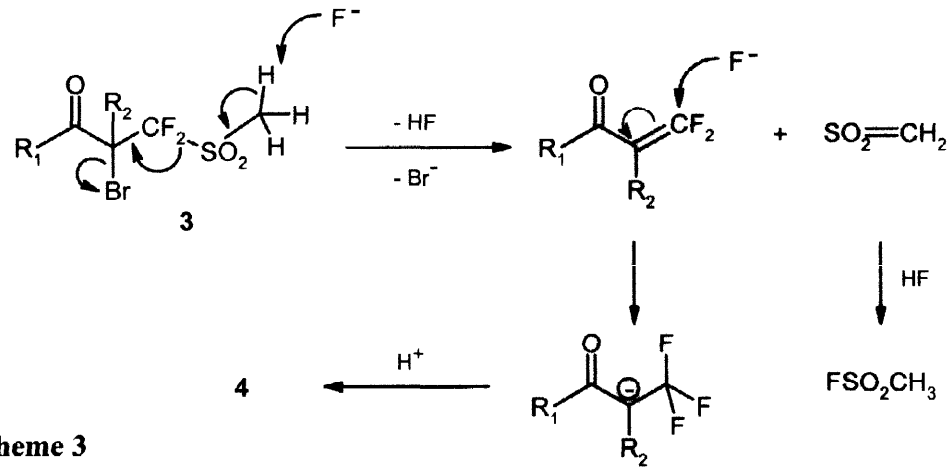
Under oxidative fluorodesulfurization conditions[14] using 1,3-dibromo-5,5-dimethylhydantoin (DBH) as the oxidising agent and the complex HF-pyridine as a source of fluorine, thioacetal **1** was smoothly converted to difluorosulfide **2**. This reaction is considered to occur *via* preliminary addition of FBr formed *in situ* to the double bond of the ketene acetal. The observed regioselectivity of this addition is that expected from the formation of the most favourable carbocationic centre stabilized by two sulfur atoms. Nucleophilic substitution of one of the thiomethyl group activated by a bromonium ion may then lead to sulfide **2** as shown in **scheme 2**. Substitution of the second sulfur atom for fluorine by this mechanism appears to be a slower process. It was thus possible to selectively stop the reaction at the monosubstitution stage by working at low temperature (-78°C)[15].

Scheme 2



Replacement of the last sulfur functionality by fluorine necessitated further activation. This was accomplished by oxidation of the sulfur atom in **2** to the sulfone stage **3** with mCPBA under standard conditions (see experimental). We were pleased to find that the resulting sulfones undergo fast and clean fragmentation reactions under the influence of fluoride anion, leading ultimately to α-trifluoromethylketones **4** and methanesulfonyl fluoride[16]. Although attack of fluoride anion at the sulfur centre[17] is conceivable and may lead to the observed products, we favour a mechanism (**scheme 3**) where this anion act as a base. This behaviour appears to be consistent with the high acidity of α-hydrogen atoms in alkyltriflones[18].

We have shown that stepwise introduction of fluorine atoms is a viable approach to the synthesis of α-trifluoromethylketones. Moreover, the rapid and straightforward base induced fragmentation reaction of difluorosulfones similar to **3** may find broader application in fluorine chemistry. We are currently examining this possibility as well as direct conversion of difluorosulfides **2** to α-bromo-α-trifluoromethylketones.



Scheme 3

Typical experimental procedure is given for the transformation of dithioacetal **1b** to the α-trifluoromethylketone **4b**.

2-Bromo-2-[difluoro(methylthio)methyl]-*p*-chloropropiophenone 2b. HF-pyridine complex (Aldrich, containing *ca.* 70% HF) (10 ml) was added dropwise to a stirred suspension of DBH (11.4 g) in dichloromethane (100 ml) cooled to -78°C. After 5 min, ketene dithioacetal **1b** (2.73 g) was added *via* a syringe. The mixture was stirred for 2 h at -78°C and the contents of the flask poured onto a mixture of ice and saturated sodium carbonate solution. After standard extractive workup with diethylether, purification of the residue by silica gel chromatography (20% CH_2Cl_2 in hexane) afforded 1.95 g (57%) of **2b** as a pale yellow oil[19].

2-Bromo-2-[difluoro(methanesulfonyl)methyl]-*p*-chloropropiophenone 3b. Conventional oxidation of sulfide **2b** (1.39 g) with mCPBA (80% grade, 1.75 g) in dichloromethane (200 ml) overnight, followed by silica gel chromatography (CH_2Cl_2) afforded 1.32 g (86 %) of **3b** as white crystals[20].

2-Trifluoromethyl-*p*-chloropropiophenone 4b. Tetrabutylammonium fluoride (Aldrich, 1.1 M solution in THF containing *ca.* 5% water) (1.45 ml) was added to a stirred solution of sulfone **3b** (300 mg) in THF (30 ml). After 10 min, the solvent was evaporated under reduced pressure and the residue eluted on a silica gel column (CH_2Cl_2) affording 150 mg (80%) of **4b** as a white solid[21].

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References and Notes

1. 'Organofluorine Chemistry. Principles and Commercial Applications'. Banks, R.E. ; Smart, B.E. ; Tatlow, J.C. Eds. *Topics in Applied Chemistry.* Plenum Press (N.Y. and London). **1994.**
2. For recent reviews see : a) McClinton, M.A. ; McClinton, D.A. *Tetrahedron Report* **1992**, *48*, 6555-6666. b) Kiselyov, A.S. ; Strekowski, L. *Org. Prep. Proced. Int.* **1996**, *28*, 289-318.
3. Cantacuzene, D. ; Wakselman, C. ; Dorme, R. *J. Chem. Soc. Perkin Trans. 1*, **1977**, 1365-1371.

4. a) Rico, I. ; Cantacuzene, D. ; Wakselman, C. *Tetrahedron Lett.* **1981**, *35*, 3405-3408. b) Tordeux, M. ; Francèse, C. ; Wakselman, C. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1951-1957.
5. **Miura, K.** ; Takeyama, Y. ; Oshima, K. ; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542-1553.
6. **Umemoto,** T. ; **Ishihara,** S. *J. Amer. Chem. Soc.* **1993**, *115*, 2156-2164.
7. **'Halon Replacements.** Technology and Science'. Miziolek A.W. ; Wing Tsang Eds. *ACS Symposium Series 611.* Amer. Chem. Soc., Washington D.C. **1995.**
8. **Dmowski,** W. 'Replacement of Sulfur by Fluorine' in 'Chemistry of Organic Fluorine Compounds II : a Critical Review' Hudlický, M. ; Pavlath, A.E. Eds. *ACS Monograph 187* Amer. Chem. Soc., Washington D.C. **1995** p. 263-270.
9. a) **Matthews,** D.P. ; Whitten, J.P. ; McCarthy, J.R. *Tetrahedron Lett.* **1986**, *27*, 4861-4864. b) Kuroboshi, M. ; Hiyama, T. *Chem. Letters* **1992**, 827-830. c) Furuta, S. ; Hiyama, T. *Synlett* **1996**, 1199-1200.
10. **Bohlmann,** R. *Tetrahedron Lett.* **1994**, *35*, 85-88.
11. For entry point reviews on ketene dithioacetals see : a) Kolb, M. *Synthesis* **1990**, 171-190. b) Junjappa, H. ; Ila, H. ; Asokan, C.V. *Tetrahedron* **1990**, *46*, 5423-5506. The thioacetals used in this work were prepared from the corresponding ketone by a slight modification[12] of the original method described by Thuillier and Vialle[13].
12. Potts, K.T. ; Ralli, P. ; Theodoridis, G. ; Winslow, P. *Org. Synth.* **1986**, *64*, 189-194.
13. Thuillier, A. ; Vialle, J. *Bull. Soc. Chim. Fr.* **1962**, 2187-2193.
14. Sondej, S.C. ; Katzenellenbogen, J.A. *J. Org. Chem.* **1986**, *51*, 3508-3513.
15. At higher temperature the reaction was less selective. We observed the formation of mixtures containing difluorosulfide **2** as well as α-bromo-α-trifluoromethylketones and others as yet unidentified fluorinated compounds.
16. Identified by ^{19}F NMR of the crude reaction mixture, δ_F = +60.6 ppm.
17. As observed for example with fluorinated sultones, see Mohtasham, J. ; Gard, G.L. *Coordination Chem. Reviews* **1992**, *112*, 47-79.
18. Hendrickson, J.B. ; Bair, K.B. ; Bergeron, R. ; Giga, A. ; Skipper, P.L. ; Sternbach, D.D. ; Wareing, J.A. *Org. Prep. Proced. Int.* **1977**, *9*, 173-207.
19. Data for **2b** : HR-MS found 341.9293 $C_{11}H_{10}{}^{79}Br^{35}ClF_2OS$ requires 341.9292 ; ^1H NMR (300 MHz, $CDCl_3$) δ 2.16 (d, 3H, $^4J_{HF}$ 1.1 Hz, Me), 2.29 (d, 3H, $^4J_{HF}$ 1.1 Hz, SMe), 7.39 and 8.08 (2xd, 2x2H, *J* 8.7 Hz, ArH) ; ^{19}F NMR (282 MHz, $CDCl_3$) AB spectrum δa -79.5, δb -74.4, *J*ab 204 Hz ; ^{13}C NMR (85 MHz, $CDCl_3$) δ 11.2 (dd, 1C, $^3J_{CF}$ 6 and 5 Hz, SCH_3), 26.4 (t, 1C, $^3J_{CF}$ 2 Hz, CH_3), 64.9 (t, 1C, *C*Br, $^2J_{CF}$ 23 Hz), 127.8 (dd, 1C, $^1J_{CF}$ 288 and 286 Hz, CF_2), 128.2 (s, 2C, Ar C_3), 132.4 (dd, 2C, $^5J_{CF}$ 3 and 1 Hz, Ar C_2), 134.3 (d, 1C, $^4J_{CF}$ 1 Hz, Ar C_1), 139.1 (s, 1C, Ar C_4-Cl), 191.4 (s, 1C, *C*=O); I.R. (CCl_4, cm^{-1}) 1593, 1684 and 1700.
20. Data for **3b** : M.p. 91.0-91.8 °C (hexane) ; HR-MS found 373.9159 $C_{11}H_{10}{}^{79}Br^{35}ClF_2O_3S$ requires 373.9161 ; ^1H NMR (300 MHz, $CDCl_3$) δ 2.32 (t, 3H, $^4J_{HF}$ 1.3 Hz, Me), 3.19 (dd, 3H, $^4J_{HF}$ 3.6 and 1.4 Hz, SO_2Me), 7.43 and 8.01 (2xd, 2x2H, *J* 8.7 Hz, ArH) ; ^{19}F NMR (282 MHz, $CDCl_3$) AB spectrum δa -97.7, δb -90.0, *J*ab 228 Hz ; ^{13}C NMR (85 MHz, $CDCl_3$) δ 24.7 (dd, 1C, $^3J_{CF}$ 4 and 2 Hz, CH_3), 39.1 (s, 1C, SO_2CH_3), 61.1 (dd, 1C, *C*Br, $^2J_{CF}$ 20 and 16 Hz), 120.6 (dd, 1C, $^1J_{CF}$ 300 and 296 Hz, CF_2), 128.6 (s, 2C, Ar C_3), 131.4 (d, 2C, $^5J_{CF}$ 2 Hz, Ar C_2), 133.1 (dd, 1C, $^4J_{CF}$ 3 and 1 Hz, Ar C_1), 139.4 (s, 1C, Ar C_4-Cl), 190.7 (dd, 1C, $^3J_{CF}$ 3 and 2 Hz , *C*=O); I.R. (CCl_4, cm^{-1}) 1591 and 1693.
21. Data for **4b** : M.p. 68.6-69.4 °C (hexane in the cold); microanalysis : found C 50.83, H 3.42, Cl 14.98, F 23.73 $C_{10}H_8ClF_3O$ requires C 50.76, H 3.41, Cl 14.98 and F 24.09%; HR-MS found 236.0216 ; $C_{10}H_8{}^{35}ClF_3O$ requires 236.0216 ; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (d, 3H, $^3J_{HH}$ 7.0 Hz, Me), 4.2 (qq, 1H, $^3J_{HF}$ 7.6 and $^3J_{HH}$ 7.0 Hz), 7.49 and 7.90 (2xd, 2x2H, *J* 8.5 Hz, ArH) ; ^{19}F NMR (282 MHz, $CDCl_3$) -68.7 (d, $^3J_{FH}$ 7.6 Hz) ; ^{13}C NMR (85 MHz, $CDCl_3$) δ 11.5 (q, 1C, $^3J_{CF}$ 3 Hz, CH_3), 44.3 (q, 1C, *C*H, $^2J_{CF}$ 27 Hz), 127.2 (q, 1C, $^1J_{CF}$ 280 Hz, CF_3), 129.2 (s, 2C, Ar C_3), 130.0 (s, 2C, Ar C_2), 134.0 (q, 1C, $^4J_{CF}$ 1 Hz, Ar C_1), 140.6 (s, 1C, Ar C_4-Cl), 193.3 (q, 1C, $^3J_{CF}$ 2 Hz, *C*=O); I.R. (CCl_4, cm^{-1}) 1602 and 1703.