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# TRIFLUOROACETALDEHYDE THIOACETALS

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## SUMMARY

Two thioacetals of trifluoroacetaldehyde have been prepared and their reactions have been studied. These compounds cannot be used for transfer of a nucleophilic trifluoromethyl acyl group to electrophiles.

## INTRODUCTION

Trifluoromethyl ketones have been shown to inhibit enzymatic reactions and are used in studies to determine the mechanism of inhibition [1]. Thus, there is a need for synthetic routes to these compounds. Aryl trifluoromethyl ketones can be prepared by a Friedel-Crafts acylation using trifluoroacetic anhydride [2] or a Hoesch synthesis [3]. However, alkyl trifluoromethylketones are less easily obtained in part because trifluoromethyl Grignard reagents that might be added to aldehydes and subsequently oxidized are difficult to prepare and give poor yields [4]. The reaction of Grignard reagents with trifluoroacetic acid gives rise to trifluoromethyl ketones accompanied by alcohols [5]. Burton and coworker [6] have recently prepared trifluoromethyl cadmium and trifluoromethyl zinc as transfer agents for the trifluoromethyl group. However, these reagents have not been used as trifluoromethyl ketone precursors. Addition of organometallic compounds to various trifluoroacetic acid derivatives gives rise to trifluoromethyl ketones albeit in low yields [7]. A more recent synthesis was devised by Linderman and Graves who oxidized trifluoromethylcarbinols with the Dess-Martin periodane reagent [8].

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RESULTS AND DISCUSSION

We sought to employ dithioacetal methodology in the synthesis of trifluoromethyl ketones [9]. Both the diphenylthioacetal (**1a**) and the dithiane of trifluoroacetaldehyde (**1b**) are readily available from the aldehyde and the thiol using polyphosphoric acid trimethylsilyl ester [10

**1a** **1b**

Interestingly, the chemical shift of the aldehydic proton of **1a** is solvent dependent. The expected quartet shifts downfield as the polarity of the solvent increases (Table 1).

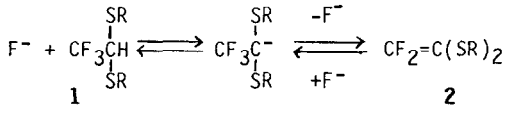
TABLE 1

$^1H$ Chemical Shifts for $CF_3CH(SR)_2$

| | 1a | 1b |
|---|---|---|
| Solvent | δ (ppm) | δ (ppm) |
| $CDCl_3$ | 4.5 | 3.98 |
| THF | 4.9 | - |
| $CD_3OD$ | 4.9 | - |
| $D_6$-DMSO | 5.7 | 4.72 |

The chemical shifts were also found to be concentration dependent.

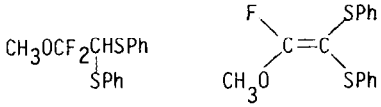
We chose fluoride ion as the base [11] to deprotonate the dithioacetal because we expected that it would suppress the elimination of fluoride ion from the dithioacetal carbanion as shown in Scheme 1.



**1** **2**

Scheme 1

Various electrophiles (benzyl bromide, butyl bromide, benzaldehyde) were included in the solution in an attempt to trap the intermediate carbanion. No reaction was observed for either dithioacetal when either tetrabutylammonium fluoride, or potassium fluoride in the presence of 18-crown-6 was used as the fluoride source. When **1a** was treated with potassium fluoride in methanol, the $^{19}F$ NMR spectrum indicated the formation of compounds **3** and **4** that show elimination of fluoride and incorporation of methoxy.

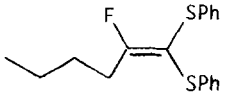


**3** **4**

In order to increase the acidity of the aldehydic proton, one sulfur in 1b was oxidized to the sulfoxide. This modification still did not facilitate the alkylation.

Alkene **2a** (R = Ph) was prepared by treatment of **1a** with 30% KOH. Treatment of this alkene with tetrabutylammonium fluoride or KF in the presence of 18-crown-6 in the presence of an electrophile either gave no reaction or the starting thioacetal from an adventitious source of water. When water was carefully excluded, no reaction was observed.

Alkenes related to **2a** and **2b** where R = $CH_2CH_3$ have been shown to react with alkyl lithiums and Grignard reagents to form monofluoro alkenes which are readily hydrolyzed to 2-fluoro carboxylic acids [12]. In a similar manner alkene **2a** (R = Ph) reacts with n-butyl lithium to form compound **5.**



**5**

EXPERIMENTAL

The $^1H$ NMR (90 MHz) and $^{19}F$ NMR (84.7 MHz) were obtained on a Varian EM-390 NMR spectrometer, and the $^{13}C$ NMR (25.18 MHz) on an IBM 100 AF-FTNMR spectrometer. Chemical shifts are reported in ppm downfield relative to internal $Me_4Si$ for $^1H$ NMR data and external $CFCl_3$ for $^{19}F$ NMR, with $CDCl_3$ as the solvent in both cases. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were

performed by Atlantic Microlab, Inc., Atlanta, GA. Column chromatography was performed with Kieselgel 60 flash silica gel. All reagents that are not referenced were commercially available from Aldrich Chemical Co.

The Diphenylthioacetal of Trifluoroacetaldehyde (**1a**)

Phosphorus pentoxide (2.84 g, 20 mmol) and hexamethyldisiloxane (2.44 g, 15 mmol) in dichloroethane (10 mL) were heated at reflux for 30 min under nitrogen [9]. To this solution, trifluoroacetaldehyde ethyl hemiacetal (0.72 g, 5.0 mmol) and thiophenol (1.10 g, 10 mmol) were added and the mixture was refluxed with stirring for 12 hrs. The resulting solution was poured into 1 M aqueous sodium hydroxide solution (200 mL), and the product extracted with dichloromethane (3 x 15 mL). The organic phase was dried ($MgSO_4$), and it was evaporated. The crude product was purified by distillation (65% yield) as a pale yellow oil: bp 116-117°C (0.3 mmHg); $^1H$ NMR ($CDCl_3$): $\delta$4.50 (q, $J_{HF}$ = 8.1 Hz, 1H), 7.20-7.65 (m, 10H). $^{19}F$ NMR ($CDCl_3$): $\phi$-68.6 (d, $J_{FH}$ = 8.1 Hz). $^{13}C$ NMR ($CDCl_3$): $\delta$ 61.21 (dq, $^1J_{CH}$ = 152.9 Hz, $^3J_{CF}$ = 30.4 Hz) 125.04 (q, $J_{CF}$ = 279.3 Hz), 125.84, 130.78, 132.11, 137.42. Anal. Calcd. for $C_{14}H_{11}F_3S_2$: C, 55.98; H, 3.69; S, 21.35. Found: C, 55.85; H, 3.73; S, 21.38.

The Dithiane of Trifluoroacetaldehyde (**1b**)

This compound was obtained as described above replacing thiophenol with 1,3-propanedithiol. The reaction took 6 hrs to go to completion. The product obtained was purified by distillation (75% yield) as a pale yellow oil: bp 60-61°C (0.6 mm Hg). $^1H$ NMR ($CDCl_3$): $\delta$ 1.90-3.30 (m, 6H), 3.88 (q, $J_{HF}$ = 9 Hz, 1H). $^{19}F$ NMR ($CDCl_3$): $\phi$ -67.2 (d, $J_{FH}$ = 9 Hz). Anal. Calcd. for $C_5H_7F_3S_2$: C, 31.91; H, 3.75; S, 34.06. Found: C, 32.18; H, 3.77; S, 33.95.

Reaction of 1a with methanol

A mixture of **1a** (1.30 g, 4.4 mmol) and KF (1.40 g, 24.3 mmol) in 10 ml MeOH was stirred at room temperature for 3 days. Water (20 mL) was added and the resulting solution was extracted with $CH_2Cl_2$ (3 x 10 mL). The organic phase was dried ($MgSO_4$) and evaporated. A mixture of **3** and **4** was obtained in a 1:6 ratio determined from $^1H$ NMR (83% yield). Column chromatography was performed (petroleum ether: $CH_2Cl_2$, 1:1) to separate the two

products. Compound **3** (12% yield): $^1$H NMR ($CDCl_3$) $\delta$ 3.65 (s, 3H), 4.55 (t, $J_{HF}$ = 6 Hz, 1H), 7.28 - 7.60 (m, 10H). $^{19}$F NMR ($CDCl_3$) $\phi$ -77.1 (d, $J_{FH}$ = 6 Hz). Anal. Calcd for $C_{15}H_{13}FOS_2$: C, 57.67; H, 4.52; S, 20.53. Found: C, 57.59; H, 4.53; S, 20.62. Compound **4** (71% yield): $^1$H NMR ($CDCl_3$) $\delta$ 3.92 (s, 3H), 7.28 (s, 10H). $^{19}$F NMR ($CDCl_3$) $\phi$ -68.8 (s).

## Oxidation of **1b** to the corresponding sulfoxide

To a solution of the dithiane **1b** (0.66 g, 3.5 mmol) in 15 mL $CH_2Cl_2$, was added dropwise a solution of MCPBA (0.71g, 3.5 mmol) in 30 ml $CH_2Cl_2$. The reaction mixture was stirred for 12 hrs at room temperature. The resulting solution was washed with 20 mL of saturated $NaHCO_3$ followed by 20 mL of $H_2O$. The organic phase was dried ($MgSO_4$) and evaporated. White crystals were obtained (80%); mp 76-78°C (from isooctane). $^1$H NMR ($CDCl_3$): $\delta$ 2.0-3.4 (m, 6H), 4.12 (q, $J_{HF}$ = 8.7 Hz, 1H). $^{19}$F NMR ($CDCl_3$): $\phi$ -64.0 (d, $J_{FH}$ = 8.7 Hz). Anal. Calcd. for $C_5H_7F_3OS_2$: C, 29.41; H, 3.45; S, 31.40. Found: C, 29.50; H, 3.49; S, 31.34.

## Preparation of alkene **2a**

To a solution of **1a** (14.41 g, 48 mmol) in 15 mL THF cooled in a water-ice bath, 5.3 M KOH (18.1 mL, 96 mmol) was added dropwise. The solution was stirred efficiently at room temperature for 6 hrs. Then $CH_2Cl_2$ (30 mL) was added and the resulting solution was extracted with $H_2O$ (3 x 25 mL). As the alkene polymerizes upon heating, purification was done by applying a vacuum (0.5 mmHg) for 30 min (62% yield). $^1$H NMR ($CDCl_3$): $\delta$ 7.30 (s). $^{19}$F NMR ($CDCl_3$) $\phi$ -70.0 (s). Anal. Calcd. for $C_{14}H_{10}F_2S_2$: C, 59.98; H, 3.60: S, 22.87. Found: C, 59.87; H, 3.61; S, 22.80.

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