

Journal of Fluorine Chemistry 80 (1996) 71-75



# The 2,4,6-tris(trifluoromethyl)phenyl group: methyl and vinyl ketones and related chemistry<sup>1</sup>

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Received 20 December 1995; accepted 23 May 1996

### Abstract

2,4,6-Tris(trifluoromethyl) phenyllithium (1) reacts with acetaldehyde and acrolein to give the corresponding alcohols 5 and 8. Oxidation of the alcohols with the  $CrO_3$ -pyridine complex affords the acetophenone 3 and the vinyl ketone 7 respectively. The reactions of 1 with trifluoroacetic anhydride and trimethylsilyl trifluoroacetate give low to moderate yields of the trifluoroacetophenone 6.

Keywords: Aryl ketones; IR spectroscopy; Mass spectrometry; NMR spectroscopy; Reactions; 2,4,6-Tris(trifluoromethyl)phenyl

# 1. Introduction

The 2,4,6-tris(trifluoromethyl)phenyl group combines steric bulk with electronic stabilization. Although the  $CF_3$ groups are electron withdrawing in relation to the aryl ring, electron donation of the lone pairs on fluorine provides stabilization of low-coordinated main group metal and metalloid derivatives [1–4]. The sterically crowded organolithium compound 1 is thermally stable and undergoes a wide range of reactions [1].

In an earlier paper [5], we reported the chemistry of 2,4,6-tris(trifluoromethyl)benzoic acid (2), the formation of its esters only via an oxocarbocation and unsuccessful attempts to prepare 2,4,6-tris(trifluoromethyl)acetophenone (3). We confirmed a previous report [1] that 3, formed by reaction of 1 with acetyl chloride, is rapidly converted to the keto-enol 4 by aldol reaction of the enolate of 3 with acetyl chloride.

In another approach to 3, the lithium carboxylate, generated by reaction of 2 with methyllithium, failed to react with excess  $CH_3Li$  to form 3. This lack of reactivity was ascribed

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to steric inhibition to the formation of the requisite tetrahedral intermediate.

# 2. Results and discussion

Further efforts to prepare 3 directly from 1 by reaction with acetic anhydride or trimethylsilyl acetate, instead of acetyl chloride, were unsuccessful. We then examined a two-step approach via the intermediate secondary alcohol. Thus 2,4,6-tris(trifluoromethyl)- $\alpha$ -methylbenzyl alcohol (5), obtained in 36% yield by reaction of 1 with acetaldehyde [6], was oxidized with the chromium trioxide-pyridine complex [7] in CH<sub>2</sub>Cl<sub>2</sub> to afford the pure ketone 3 in 61% yield, as summarized in Scheme 1. An attempt to prepare 3 by Swern oxidation (DMSO-trifluoroacetic anhydride) [8] of 5 was



<sup>&</sup>lt;sup>1</sup> Dedicated to Professor Alois Haas on the occasion of his 65th birthday.

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unsuccessful, perhaps due to steric inhibition to the formation of the alkylsulfonium trifluoroacetate intermediate.

In contrast with acetic anhydride, trifluoroacetic anhydride and **1** react to give a low yield of the trifluoroacetophenone **6**, isolated as its hydrate **6a**. The free ketone, which exhibits an exceptionally high carbonyl frequency ( $\nu_{C=0} = 1787$ cm<sup>-1</sup>) due to the flanking CF<sub>3</sub> groups, was obtained when the hydrate was passed through a column of silica. Compound **6** was also prepared in 42% yield from **1** and trimethylsilyl trifluoroacetate. The reactions are shown in Scheme 2.

Since hindered achiral ketones, such as trifluoroacetylmesitylene, are readily reduced to enantiomerically pure secondary alcohols [9], ketones **3** and **6** may be of considerable synthetic interest.

Another objective of this study was the preparation of the aryl vinyl ketone 7, which cannot undergo the aldol condensation observed with 3. The reaction of 1 with acryloyl chloride gave a mixture of products including a low yield (11%) of 7. The predominant product (29%) was the saturated "dimeric" ketone 9, formed by rapid Michael addition of the strong nucleophile 1 to the initially formed 7 (Scheme 3).

In a sequence analogous to the preparation of the acetophenone 3, 7 was obtained in two steps. Reaction of 1 with acrolein provided a 33% yield of 2,4,6-tris(trifluoromethyl)- $\alpha$ -vinyl benzyl alcohol (8). Oxidation with CrO<sub>3</sub>-pyridine gave a 50% yield of 7 (Scheme 4).

All of the new ketones were fully characterized by elemental and/or mass spectral analyses and IR and <sup>1</sup>H NMR spectroscopy.

### 3. Experimental details

Elemental analyses were conducted by Midwest Microlab, 7212 N. Shadeland Ave., Indianapolis, IN, USA.

Melting points were measured by an electric thermal melting point apparatus (Mel-Thermal), and all melting points are uncorrected.

Proton and <sup>13</sup>C magnetic resonance spectra were recorded on a Bruker 200 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as internal standard.

IR spectra were recorded on a Nicolet 5MX FT IR spectrometer. Mass spectra were obtained with a Perkin–Elmer Q-Mass 910 mass spectrometer.

#### 3.1. 2,4,6-Tris(trifluoromethyl)- $\alpha$ -methylbenzyl alcohol (5)

A solution of 1,3,5-tris(trifluoromethyl)benzene (10 g, 35.45 mmol) in anhydrous diethyl ether (20 ml) was placed in a 250 ml, three-necked flask. The flask was equipped with a magnetic stirrer, a gas inlet, a dropping funnel and a condenser carrying a calcium sulfate drying tube at the top. The flask was immersed in a 20 °C water bath. A solution of nbutyllithium in hexanes (1.6 M, 23.00 ml, 36.8 mmol) was added dropwise with stirring under nitrogen. An exothermic reaction occurred throughout the addition. The color in the flask became vellow. When no further reaction was observed. the mixture was heated at reflux for 30 min and then cooled in an ice bath. A solution of acetaldehyde (1.56 g, 35.45 mmol) in anhydrous diethyl ether (20 ml) was added slowly. No apparent reaction occurred on mixing. The mixture was heated under reflux for 30 min after the addition was complete. The mixture turned bright orange and was then hydrolyzed with 50 ml of water and neutralized with 1 M HCl. The ether layer was separated and the water layer was extracted with ether (50 ml $\times$ 2). The combined ether layers were washed with water (50 ml $\times$ 2) and dried over anhydrous magnesium sulfate. The ether was removed on a Rotavapor and the residual brown oil was distilled to yield 2,4,6tris(trifluoromethyl)- $\alpha$ -methylbenzyl alcohol (4.16 g, 12.76 mmol, 36%). B.p., 71-72 °C (4 Torr). M.p., 53-54 °C (54-55 °C [6]).

The <sup>1</sup>H NMR spectrum in chloroform-*d* revealed a doublet at  $\delta$  1.64 (3H), a singlet at  $\delta$  8.17 (2H), a quintet at  $\delta$  5.60 (1H) and a broad peak at  $\delta$  2.90. The IR spectrum in carbon tetrachloride revealed bands at 3450 cm<sup>-1</sup> (s, O–H), 1580 cm<sup>-1</sup> (w, aromatic C=C) and 1150 cm<sup>-1</sup> (s, C–F).

#### 3.2. Chromium trioxide-pyridine complex

Chromium trioxide was stored in a vacuum desiccator over phosphorus pentoxide for 24 h. Anhydrous pyridine, prepared by distillation of reagent grade material from barium oxide, was stored over 4 Å molecular sieves. Dichloromethane was washed with 10 M sulfuric acid, 3 M sodium hydroxide and water, dried over anhydrous potassium carbonate and distilled. Chromium trioxide (2.50 g, 25.0 mmol) was placed in a three-necked, round-bottomed flask which was equipped with a magnetic stirrer, a dropping funnel and a condenser carrying a CaCl<sub>2</sub> drying tube at the top. Anhydrous pyridine (25 ml) was added slowly to the flask with stirring while the temperature was maintained below 30 °C. The mixture was treated with 100 ml of hexanes and quickly filtered under reduced pressure. The orange solid was washed with hexanes to yield the complex (3.58 g, 20.0 mmol, 80%) [7].

#### 3.3. 2,4,6-Tris(trifluoromethyl)acetophenone (3) (nc)

# 3.3.1. Method A

A solution of chromium trioxide-pyridine complex (3.58 g, 20.0 mmol) in anhydrous dichloromethane (50.0 ml) was placed in a 250 ml, three-necked flask. The flask was equipped with a dropping funnel, a condenser carrying a drying tube at the top and a magnetic stirrer. A solution of 2,4,6-tris(trifluoromethyl)- $\alpha$ -methylbenzyl alcohol (5) (1.0 g, 3.06 mmol) in anhydrous dichloromethane (20.0 ml) was added in one portion. There was no reaction at room temperature. The mixture was heated under reflux and the color turned from orange to black with some tar formation. After refluxing for 12 h, the mixture was cooled in an ice bath. Water (20 ml) was added to the mixture and the pH was adjusted to about 8.0 by adding 5 M sodium hydroxide. The organic layer was separated and the green water layer was extracted with dichloromethane (50 ml $\times$ 2). The combined organic layers were washed successively with 0.1 M sodium hydroxide solution (30 ml $\times$ 2), 0.1 M sulfuric acid (30  $ml \times 2$ ) and water (30 ml  $\times 2$ ), and dried over anhydrous magnesium sulfate. The solvent was removed on a Rotavapor and a brown oil remained in the flask. This oil was passed through a column of silica gel (70-230 mesh, 60 Å) using hexanes-chloroform (87:13) as eluent to give a white solid after removal of the solvent. This solid sublimated at 60 °C (1.0 Torr) to yield 2,4,6-tris(trifluoromethyl)acetophenone as white crystals (0.60 g, 1.85 mmol, 61%). M.p., 67-69 °C. Analysis: calculated: C, 40.67%; H, 1.55%; found: C, 40.59%; H, 1.50%. Mass spectrum: m/z 324 [M], 309 (M-CH<sub>3</sub>), 281 (M-COCH<sub>3</sub>), 43 (CH<sub>3</sub>CO).

The <sup>1</sup>H NMR spectrum in chloroform-*d* revealed singlets at  $\delta 2.60$  (3H) and  $\delta 8.20$  (2H). The IR spectrum in carbon tetrachloride showed bands at 1720 cm<sup>-1</sup> (s, C=O), 1550 cm<sup>-1</sup> (m, aromatic ring C=C) and 1160 cm<sup>-1</sup> (s, C=F).

#### 3.3.2. Method B

A solution of dry dimethylsulfoxide (DMSO, 0.71 ml, 10.0 mmol) in anhydrous dichloromethane (15 ml) was placed into a dry 250 ml, three-necked flask. The flask was immersed in a dry ice-acetone bath and equipped with a magnetic stirrer, a dropping funnel and a condenser carrying a calcium sulfate drying tube at the top. A solution of trifluoroacetic anhydride (3.15 g, 15.0 mmol) in anhydrous dichloromethane (10 ml) was added slowly with efficient mechanical stirring during 15 min. The mixture was stirred at -78 °C for an additional 15 min. A solution of 2,4,6tris(trifluoromethyl)- $\alpha$ -methylbenzyl alcohol (1.23 g, 3.77 mmol) in anhydrous dichloromethane (10 ml) was added dropwise to the mixture during 15 min. The rate of addition of both the trifluoroacetic anhydride and the alcohol was controlled to keep the temperature below -65 °C. The mixture was stirred at -78 °C for 30 min, followed by addition of anhydrous triethylamine (2.0 ml) dropwise during 15 min. The temperature was maintained at -78 °C until the addition of the triethylamine was completed. The cooling bath was then removed and the reaction mixture was allowed to warm to room temperature; the mixture was washed with water (20 ml) and the aqueous layer was extracted with dichloromethane  $(10 \text{ ml} \times 2)$ . The combined organic layers were washed with water  $(10 \text{ ml} \times 2)$  and the solvent was removed to give a white paste. The IR spectrum of this crude material showed no carbonyl absorption.

# 3.4. 2,4,6-Tris(trifluoromethyl)- $\alpha$ -vinylbenzyl alcohol (8) (nc)

A solution of 1,3,5-tris(trifluoromethyl)benzene (10.14 g, 35.95 mmol) in anhydrous diethyl ether (20 ml) was placed in a 250 ml, three-necked flask. The flask was equipped with a magnetic stirrer, a gas inlet, a dropping funnel and a condenser carrying a calcium sulfate drying tube at the top. The flask was immersed in a 30 °C water bath. A solution of nbutyllithium in hexanes (1.6 M, 23.5 ml, 37.6 mmol) was added slowly through the funnel under a moderate flow rate of nitrogen. An exothermic reaction occurred throughout the addition and the mixture became yellow. When no further reaction was apparent, the mixture was refluxed for an additional 15 min and then cooled in an ice bath. The flask was wrapped with aluminum foil to avoid light in order to minimize polymerization in the subsequent reaction. A solution of acrolein (2.5 g, 44.59 mmol) in anhydrous diethyl ether (20 ml) was added dropwise to the solution at 0 °C. The mixture was stirred for 1 h at 0 °C. The ice bath was removed and the mixture was stirred for an additional 12 h at room temperature. The color intensified to pale orange. The mixture was heated under reflux for 1 h before hydrolysis with water (30 ml). The hydrolyzed mixture was neutralized with 3 M sulfuric acid. The ether layer was separated and the aqueous layer was extracted with diethyl ether (75 ml  $\times$  2). The combined ether layers were washed with water  $(70 \text{ ml} \times 2)$ , dried over anhydrous magnesium sulfate and the solvent was

removed to give a brown oil. Half of the brown oil was distilled to yield 2,4,6-tris(trifluoromethyl)- $\alpha$ -vinylbenzyl alcohol as a light yellow liquid. B.p., 90-91 °C (2.5 Torr). The other half of the brown oil was run through a silica gel column (70-230 mcsh, 60 Å) using 10 ml hexanes-chloroform (90:10) as eluent. After the first fraction was removed, chloroform-ethyl acetate (9:2) was used. The second fraction, determined by thin layer chromatography (TLC), was collected and the solvent was removed to give 2,4,6tris(trifluoromethyl)- $\alpha$ -vinylbenzyl alcohol as a yellow liquid. Total yield, 2.0 g, 11.8 mmol, 33%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 5.93 (t, 1H), 6.15 (m, 1H), 5.20 (two doublets, 2H), 8.19 (s, 2H). <sup>13</sup>C NMR δ: 70.5 (s), 117.7 (s), 138.0 (s), 145.3 (s), 121.5 (d), 124.3 (d), 127.8 (d), 131.0 (m). IR (CCl<sub>4</sub>): 3400 (s, O-H), 1630 (s, terminal C=C), 1585 (s, aromatic C=C, 1120 (s, C-F) cm<sup>-1</sup>.

# 3.5. [2,4,6-Tris(trifluoromethyl)phenyl]vinyl ketone (7) (nc)

A solution of fresh chromium trioxide-pyridine complex (1.60 g, 8.94 mmol) in anhydrous dichloromethane (50 ml) was placed in a 250 ml, three-necked flask. The flask was equipped with a dropping funnel, a magnetic stirrer and a condenser carrying a drying tube at the top. The flask was wrapped with aluminum foil to avoid light. A solution of 2,4,6-tris(trifluoromethyl)- $\alpha$ -vinylbenzyl alcohol (1.0 g, 2.96 mmol) in anhydrous dichloromethane (20 ml) was added in one portion. There was no reaction at room temperature and the mixture was heated at reflux. The color turned from orange to black with some tar formation. After 12 h of reflux, the mixture was cooled with an ice bath. Sodium hydroxide solution (5%, 50 ml) was added to the mixture. The organic layer was separated and the black tarry aqueous layer was extracted with dichloromethane  $(50 \text{ ml} \times 2)$ . The combined organic layers were washed with 0.1 M sodium hydroxide solution (30 ml), 0.1 M sulfuric acid  $(30 \text{ ml} \times 2)$ and water  $(30 \text{ ml} \times 2)$ , and dried over anhydrous magnesium sulfate. The solvent was removed on a Rotavapor. A brown oil remained in the flask and froze in a cold water bath. The oil was run through a silica gel column (70–230 mesh, 60 Å) using hexane-chiloroform (11:1) as eluent. The second fraction, determined by TLC, was collected and the solvent was removed to yield a white solid. This solid sublimated at room temperature Torr) give (1 to [2,4,6tris(trifluoromethyl)phenyl]vinyl ketone (0.50 g, 1.49 mmol, 50%) as white crystals. M.p. 55-56 °C. Analysis: calculated: C, 42.87%; H, 1.50%; found: C, 43.18%; H, 1.48%. Mass spectrum: m/z 336 [M], 309 (M – CH=CH<sub>2</sub>),  $(M - COCH = CH_2),$  $(281 - CF_3),$ 281 212 143  $(281 - 2CF_3)$ . <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ : 8.18 (s, 2H), 6.25 (d, 1H), 5.90 (d, 1H), 6.70 (doublet of doublets, 1H). FT IR  $(CCl_4)$ : 1694 (s,  $\alpha,\beta$ -unsaturated C=0), 1587, 1154 cm<sup>-1</sup>. 3.6. 2,4,6-Tris(trifluoromethyl)trifluoroacetophenone (6) (nc)

#### 3.6.1. Method A

To a solution of 1,3,5-tris(trifluoromethyl)benzene (4.0 g, 14.18 mmol) in dry ether (40 ml) at -70 °C was added n-butyllithium (2.5 M, 5.93 ml, 14.83 mmol) dropwise with stirring, under nitrogen, during 10 min. Stirring was continued for 2 h and, after the solution had reached room temperature, for an additional 3 h. The solution was cooled to -10°C and trifluoroacetic anhydride (2.28 ml, 16.31 mmol) in 10 ml of ether was added. The mixture was stirred for 45 min and then poured into 20 ml of ice-cold water and acidified with dilute HCl. The ether layer was dried over MgSO4 and a yellow liquid was obtained after removal of ether. FT IR:  $v_{\rm OH} = 3423$  (s, broad) cm<sup>-1</sup>, no band in 1800–1700 cm<sup>-1</sup> region for C=O. The liquid was passed through a column of silica gel (70–230 mesh, 60 Å) using ether as eluent to give 1.17 g (20%) of a light yellow liquid. B.p., 112-116 °C (10 Torr). FT IR:  $\nu_{C=O} = 1787 \text{ cm}^{-1}$  (no O–H band).

### 3.6.2. Method B

The same procedure as described in method A was followed, except that trimethylsilyl trifluoroacetate (3.0 ml, 16.31 mmol) was used instead of trifluoroacetic anhydride. The yield of **6** was 2.27 g (42%). FT IR:  $\nu_{C=O} = 1787 \text{ cm}^{-1}$ . Mass spectrum: m/z 378 [M], 309 (M-CF<sub>3</sub>), 281 (M-COCF<sub>3</sub>).

# 3.7. [2,4,6-Tris(trifluoromethyl)phenyl]vinyl ketone (7) and Michael addition product (9) (nc)

To a solution of 1,3,5-tris(trifluoromethyl)benzene (4.0 g, 14.18 mmol) in dry ether (40 ml) at -70 °C was added *n*-butyllithium (2.5 M, 5.93 ml, 14.83 mmol) dropwise with stirring, under nitrogen, during 10 min. Stirring was continued for 2 h and, after the solution had reached room temperature, for an additional 3 h. The solution was cooled to -10°C and acryloyl chloride (1.46 ml, 18 mmol) in 10 ml of ether was added. The mixture was stirred for 1 h and then heated under reflux for 2 h. The ethereal solution was acidified with dilute HCl, washed with water  $(3 \times 10 \text{ ml})$  and dried over MgSO<sub>4</sub>. After removal of ether, the resulting gummy solid was placed on silica gel (70-230 mesh, 60 Å) and eluted, first with hexane-CHCl<sub>3</sub> (9:1), followed by a gradual increase in  $CHCl_3$  to a ratio of 1 : 1. Two products were isolated: (1) compound 7, 0.53 g (11%), m.p. 55-57 °C; (2) compound 9, white crystals, 1.27 g (29%), m.p. 97-100 °C.  $\nu_{C=0} = 1767 \text{ cm}^{-1}$ . <sup>1</sup>H NMR  $\delta$ : 8.13 (m, 4H), 1.22 (m, 2H), 0.88 (m, 2H). Mass spectrum: m/z 618 [M], 309  $(C_{6}H_{2}(CF_{3})_{3}C=0$ and  $C_6H_2(CF_3)_3CH_2CH_2)$ , 295  $((C_6H_2)(CF_3)_3CH_2), 281((C_6H_2)(CF_3)_3).$ 

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