

# A trifluoromethyl group directed semipinacol rearrangement: synthesis of $\alpha$ -(trifluoroacetyl) diarylmethanes

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## Abstract

Semipinacol rearrangements of trifluoromethyl substituted vic-diol monomethyl ethers proceeded smoothly to give  $\alpha$ -(trifluoroacetyl) diarylmethanes in good yields. The trifluoromethyl group gave specific orientation to the course of the rearrangement. © 1997 Elsevier Science S.A.

**Keywords:** Pinacol rearrangement; Semipinacol rearrangement;  $\alpha$ -(Trifluoroacetyl) diarylmethanes

## 1. Introduction

In the course of our efforts to explore new trifluoromethylated building blocks [1] we found that treatment of a benzene solution of vic-diol monomethyl ether **1a** with concentrated sulfuric acid at ambient temperature afforded  $\alpha$ -(trifluoroacetyl) diphenylmethane **2a** in 87% yield, presumably via a semipinacol rearrangement (Scheme 1) [2–4]. The term ‘semipinacol rearrangement’ has come to represent also all 1,2-migrations of 2-hetero-substituted alcohols related to pinacol rearrangement [4].

In this paper we report the synthesis of vic-diol monoethers **1a–1c** containing substituents with various electronic qualities at the *p*-position of the phenyl ring attached to the secondary carbon and their rearrangement to  $\alpha$ -(trifluoroacetyl) diarylmethanes **2a–2c**.

## 2. Results and discussion

Compounds **1** have been prepared conveniently from the easily available ‘Mosher’s nitrile’ **3** [5] (Scheme 2). Grignard reactions of compound **3** with arylmagnesium bromides afforded ketones **4**. Sodium borohydride reduction of ketones **4** gave mixtures of diastereomeric vic-glycol mono-

methyl ethers **1** (Scheme 2). The reaction conditions employed for compound **1a** were also suitable for the similar transformations of substrates **1b** and **1c** to the corresponding ketones **2b** and **2c**.

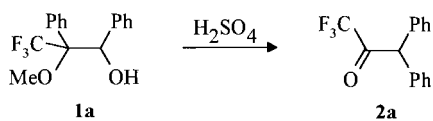
The course of the rearrangement can be explained by comparing the stabilities of the possible carbenium ion intermediates (Scheme 3). The tertiary carbenium ion **5** is destabilized by the electron-withdrawing trifluoromethyl group, therefore the formation of the secondary carbenium ion **6** is favored. 1,2-shift of the phenyl group is supposed to be accompanied by simultaneous demethylation of the ether group, thus avoiding the formation of  $\alpha$ -trifluoromethyl substituted carbenium ion **7**. A concerted rearrangement of the protonated molecule **8** also cannot be excluded.

To the best of our knowledge this is the first observation of a trifluoromethyl group controlled pinacol type (semipinacol) rearrangement. Furthermore, the reaction sequence discussed represents a convenient synthesis of trifluoroacetylated diarylmethanes from the easily available Mosher’s nitrile.

## 3. Experimental details

The melting points were determined on a Büchi 535 apparatus and are uncorrected. The IR spectra were recorded on an Aspect 2000 computer controlled Bruker IFS-113v vacuum optic FT spectrometer, using KBr pellets for solids or liquid films. The NMR spectra were run on a Bruker WM-

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Scheme 1.

250 FT, or a Varian Gemini-200, or a Varian Unity Inova 400 spectrometer. Mass spectra were obtained by EI (70 eV, evaporation temperature 120 °C) using a KRATOS MS 902 mass spectrometer.

### 3.1. Preparation of 3,3,3-trifluoro-2-methoxy-1-aryl-2-phenylpropan-1-ones (**4**): general procedure

In a typical experiment  $\alpha$ -trifluoromethyl- $\alpha$ -methoxyphenylacetonitrile (**3**, 29.0 g, 130 mmol) was added to a solution of phenylmagnesium bromide (prepared from magnesium (4.6 g, 192 mmol) and bromobenzene (17.0 ml, 29.0 g, 135 mmol) in ether (150 ml)) and the mixture was refluxed for 5 h. The solvent was evaporated and the residue was dissolved in ethanol (550 ml). Water (30 ml) and concentrated hydrochloric acid (30 ml) were added and the mixture was refluxed for 5 h. After evaporation of the ethanol, water (90 ml) was added and the pH was adjusted to 8 with aqueous sodium hydroxide (40%) solution. The mixture was extracted with ether (3  $\times$  150 ml), the combined ethereal solution was extracted with brine, dried on magnesium sulfate and evaporated. The residual oil was distilled to give 3,3,3-trifluoro-2-methoxy-1,2-diphenylpropan-1-one (**4a**). The physical and spectral data of compounds **4** are shown in Table 1.

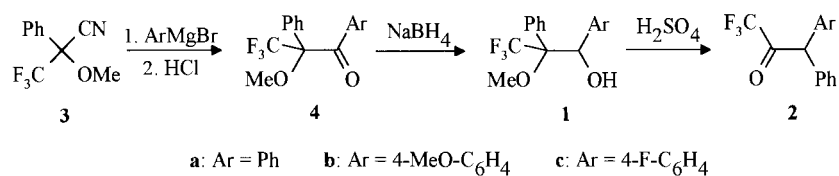
### 3.2. Preparation of 3,3,3-trifluoro-2-methoxy-1-aryl-2-phenylpropanols (**1**): general procedure

In a typical experiment 3,3,3-trifluoro-2-methoxy-1,2-diphenylpropan-1-one (**4a**, 29.7 g, 101 mmol) was dissolved in ethanol (450 ml) and sodium borohydride (17.8 g, 468 mmol) was added to the stirred solution. It was refluxed for 20 min, acidified by addition of aqueous hydrogen chloride solution (10%) to pH 6 and evaporated. Water (600 ml) was added to the residue and the mixture was extracted with dichloromethane (3  $\times$  300 ml), treated with charcoal and evaporated to give **1a** (29.6 g, 99%). The product was shown by its <sup>1</sup>H NMR spectrum to be a practically pure 2:1 mixture of the two diastereomers and was subjected to the semipinacol rearrangement without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$ : 7.42–6.72 (10H, m), 4.95 (1H, bs), 3.42 and 3.36 (3H, ratio ca. 1:2, 2  $\times$  q, <sup>5</sup>J<sub>HF</sub> = 1.8 Hz, through space coupling), 3.20 and 3.00 (1H, ratio ca. 1:2, bs); high resolution MS (EI) calculated for C<sub>16</sub>H<sub>15</sub>F<sub>3</sub>O<sub>2</sub> (M<sup>+</sup>) *m/z* 296.1024, found 296.1027.

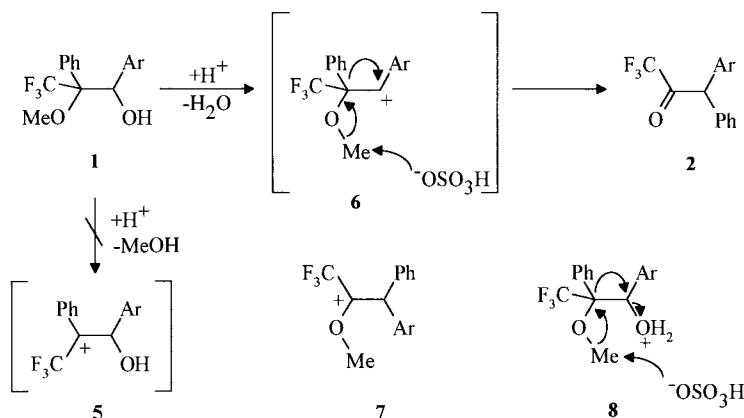
Compounds **1b** and **1c** were prepared by a similar procedure.

3,3,3-Trifluoro-2-methoxy-1-(4-methoxyphenyl)-2-phenylpropanol (**1b**): yield 99%, 4:1 mixture of the two diastereomers. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 250 MHz)  $\delta$ : 7.55–6.55 (9H, m), 4.92 (1H, bs), 3.77 and 3.73 (3H, ratio ca. 1:4, 2  $\times$  s), 3.46 and 3.42 (3H, ratio ca. 1:4, 2  $\times$  q, <sup>5</sup>J<sub>HF</sub> = 1.8 Hz, through space coupling), 4.02 and 3.81 (1H, ratio ca. 1:4, 2  $\times$  d, *J* = 6.5 and 5.0 Hz); high resolution MS (EI) calculated for C<sub>17</sub>H<sub>17</sub>F<sub>3</sub>O<sub>3</sub> (M<sup>+</sup>) *m/z* 326.1130, found 326.1123.

3,3,3-Trifluoro-1-(4-fluorophenyl)-2-methoxy-2-phenylpropanol (**1c**): yield 92%, 3:1 mixture of the two diastereomers. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$ : 7.45–6.75 (9H, m),



Scheme 2.



Scheme 3.

Table 1

Yields, boiling points, IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and high resolution MS spectra of **2** and **4**

Entry	Boiling point ( $^{\circ}\text{C}$ (mmHg))	Yield (%)	Spectrum		$\nu$ ( $\text{cm}^{-1}$ ) or $\delta$ (ppm) or exact mass ( $\text{M}^+$ , $m/z$ )
<b>2a</b>	84–86 (0.2)	87%	IR	KBr	1763
			$^1\text{H}$ NMR	400 MHz	7.38–7.17 (10H, m), 5.52 (1H, s)
			$^{13}\text{C}$ NMR	50.3 MHz	190.0 (q, $^2J_{\text{CF}} = 34$ Hz), 135.6, 129.1, 128.9, 128.1, 116.0 (q, $^1J_{\text{CF}} = 294$ Hz), 57.8
<b>2b</b>	108–110 (0.2)	71%	HRMS	EI	calculated for $\text{C}_{15}\text{H}_{11}\text{F}_3\text{O}$ 264.0762, found 264.0753
			IR	KBr	1730
			$^1\text{H}$ NMR	400 MHz	7.46–7.20 (5H, m), 7.16 (2H, d, $J = 8.4$ Hz), 6.88 (2H, d, $J = 8.4$ Hz), 5.46 (1H, s), 3.79 (3H, s)
<b>2c</b>	76–78 (0.1)	83%	$^{13}\text{C}$ NMR	100.6 MHz	190.0 (q, $^2J_{\text{CF}} = 33.6$ Hz), 159.4, 136.0, 130.0, 129.0, 128.7, 128.0, 127.4, 116.0 (q, $^1J_{\text{CF}} = 293.7$ Hz), 114.5, 57.0, 55.3
			HRMS	EI	calculated for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{O}_2$ 294.0868, found 294.0874
			IR	KBr	1764
<b>4a</b>	109–110 (0.1)	77%	$^1\text{H}$ NMR	200 MHz	7.42–7.30 (3H, m), 7.29–7.15 (4H, m), 7.03 (2H, t-like m, $J = 8.7$ Hz), 5.51 (1H, s)
			$^{13}\text{C}$ NMR	50.3 MHz	189.8 (q, $^2J_{\text{CF}} = 34.4$ Hz), 162.6 (d, $^1J_{\text{CF}} = 248$ Hz), 135.4, 131.5 (d, $^4J_{\text{CF}} = 3.4$ Hz), 130.6 (d, $^3J_{\text{CF}} = 8.4$ Hz), 129.2, 128.8, 128.3, 116.0 (q, $^1J_{\text{CF}} = 294$ Hz), 116.0 (d, $^2J_{\text{CF}} = 21.7$ Hz), 57.0
			HRMS	EI	calculated for $\text{C}_{15}\text{H}_{10}\text{F}_4\text{O}$ 282.0668, found 282.0857
<b>4b</b>	128–130 (0.2)	75%	IR	KBr	1670
			$^1\text{H}$ NMR	250 MHz	7.95–7.80 (2H, m), 7.65–7.22 (8H, m), 3.53 (3H, q, $^5J_{\text{HF}} = 1.8$ Hz, through space coupling)
			$^{13}\text{C}$ NMR	62.9 MHz	193.6, 133.9, 133.8, 133.7, 130.1, 129.5, 128.6, 128.5, 128.3, 127.4, 126.8, 123.7 (q, $^1J_{\text{CF}} = 292$ Hz), 87.0 (q, $^2J_{\text{CF}} = 25$ Hz), 56.2
<b>4c</b>	102–104 (0.2)	55%	HRMS	EI	calculated for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{O}_2$ 294.0868, found 294.0869
			IR	KBr	1650
			$^1\text{H}$ NMR	400 MHz	7.91 (2H, d, $J = 9.0$ Hz), 7.54 (2H, m), 7.35 (3H, m), 6.77 (2H, d, $J = 9.0$ Hz), 3.78 (3H, s), 3.55 (3H, q, $^5J_{\text{HF}} = 1.7$ Hz, through space coupling)
<b>4c</b>	102–104 (0.2)	55%	$^{13}\text{C}$ NMR	50.3 MHz	192.0, 163.8, 134.3, 132.6, 129.3, 128.5, 126.8, 126.7, 123.8 (q, $^1J_{\text{CF}} = 291$ Hz), 113.7, 86.8 (q, $^2J_{\text{CF}} = 25$ Hz), 56.0 (q, $^4J_{\text{CF}} = 2.3$ Hz), 55.3
			HRMS	EI	calculated for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{O}_3$ 324.0973, found 324.0964
			IR	KBr	1692
<b>4c</b>	102–104 (0.2)	55%	$^1\text{H}$ NMR	200 MHz	7.91 (2H, dd-like m, $J = 9.2$ and $5.6$ Hz), 7.58–7.48 (2H, m), 7.42–7.32 (3H, m), 6.98 (2H, t-like m, $J = 8.7$ Hz), 3.55 (3H, q, $^5J_{\text{HF}} = 1.8$ Hz, through space coupling)
			$^{13}\text{C}$ NMR	50.3 MHz	192.1, 165.9 (d, $^1J_{\text{CF}} = 257$ Hz), 133.8, 133.0 (d, $^3J_{\text{CF}} = 9$ Hz), 130.1, 129.6, 128.6, 126.8, 123.6 (q, $^1J_{\text{CF}} = 291$ Hz), 115.7 (d, $^2J_{\text{CF}} = 22$ Hz), 86.8 (q, $^2J_{\text{CF}} = 25$ Hz), 56.1 (q, $^4J_{\text{CF}} = 2$ Hz)
			HRMS	EI	calculated for $\text{C}_{16}\text{H}_{12}\text{F}_4\text{O}_2$ 312.0773, found 312.0783

4.97 (1H, bs), 3.47 and 3.40 (3H, ratio ca. 1:3,  $2 \times q$ ,  $^5J_{\text{HF}} = 1.8$  Hz, through space coupling), 3.08 and 2.91 (1H, ratio ca. 1:3,  $2 \times d$ ,  $J = 7.0$  and  $2.9$  Hz); high resolution MS (EI) calculated for  $\text{C}_{16}\text{H}_{14}\text{F}_4\text{O}_2$  ( $\text{M}^+$ )  $m/z$  314.0930, found 314.0925.

### 3.3. Preparation of 1,1,1-trifluoro-3-aryl-3-phenylpropan-2-ones (**2**): general procedure

In a typical experiment 3,3,3-trifluoro-2-methoxy-1,2-diphenylpropanol (**1a**, 29.5 g, 100 mmol, a mixture of two diastereomers, obtained as described above) was dissolved in benzene (250 ml) and concentrated sulfuric acid (16 ml) was added. After 30 min at ambient temperature the mixture was extracted with water ( $2 \times 50$  ml) and brine (50 ml), dried (magnesium sulfate) and evaporated. The residual oil

was distilled to give 1,1,1-trifluoro-3,3-diphenylpropan-2-one (**2a**). The physical and spectral data of compounds **2** are shown in Table 1.

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