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Diethyl 3-bromo-3,3-difluoropropyl acetal: preparation and SnCl₄-promoted cross-coupling reaction with trimethylsilyl enol ethers

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Abstract

The radical addition of dibromodifluoromethane to ethyl vinyl ether in ethanol under $Na_2S_2O_4$ initiation affords diethyl 3-bromo-3,3difluoropropyl acetal (1) in high yield. SnCl₄-promoted cross-coupling reaction of 1 with trimethylsilyl enol ethers (2) yield γ -bromodifluoromethyl- β -ethoxy ketones (3). © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Difluoromethylene; Trimethylsilyl enol ethers; Cross-coupling

1. Introduction

The incorporation of diffuoromethylene (CF₂) into an organic molecule has been receiving considerable attention due to the well-known feature that fluorine may confer biological active nature to molecules [1-3]. Many CF₂containing molecules have been reported to have biological activities [4-6], and great efforts have been made for the exploration of practical and effective methods to synthesize organic compounds containing difluoromethylene group. Fluorinating reagents have been widely used for incorporating CF_2 unit into a molecule [7], however, most of such reagents are not only expensive and difficult to be prepared, but also are limited to functional groups compatible with the reactive reagents. Another approach is to synthesize intermediates containing CF2 group and use them as the synthons [8], which is becoming the main tendency for construction of the CF₂-containing compound, because it usually accesses the target molecule under mild condition. Therefore, the development of an efficient and convenient method for the synthesis of CF₂-containing building block is highly desirable. Herein, an efficient general route to 3-bromo-3,3difluoropropyl acetal (1) and SnCl₄-promoted cross-coupling reaction of 1 with trimethylsilyl enol ethers (2) were described.

2. Results and discussions

Wakselman reported [9,10] the preparation of diethyl 3bromo-3,3-difluoropropyl acetal (1) through the condensation of dibromodifluoromethane and ethyl vinyl ether under UV irradiation, followed by the treatment with ethanol. However, the overall yield (two steps) is 65% and the first step is not convenient due to the difficulty in handing reactive and volatile substrates (the boiling points of dibromodifluoromethane and ethyl vinyl ether are 22 and 23°C, respectively). We developed a convenient and practical synthesis of 1 in 81% yield from the radical addition of dibromodifluoromethane to ethyl vinyl ether under Na₂S₂O₄ initiation (Scheme 1) [11–14]. Ethanol was used as a solvent and the reaction was accomplished in 5 h.

With a convenient route to diethyl 3-bromo-3,3-difluoropropyl acetal (1) in hand and based on the extensively studied reactivities of acetals [15], we attempted the reaction of 1 with trimethylsilyl enol ethers in the presence of SnCl₄ to prepare γ -bromodifluoromethyl- β -ethoxy ketones which are a kind of highly functionalized molecules containing a BrCF₂ group. The reaction succeeds in a series of trimethylsilyl enol ethers (Scheme 2), and γ -bromodifluoromethyl- β ethoxy ketones (3) are obtained in good yields. The results are listed in Table 1.

 $CF_2Br_2 + CH_2 = CHOEt \xrightarrow{Na_2S_2O_4/NaHCO_3} Br CF_2CH_2CH(OEt)_2$ 1

Scheme 1

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Scheme 2

Table 1 Reactions of diethyl 3-bromo-3,3-difluoropropyl acetal with trimethylsilyl enol ethers in the presence of SnCl₄

Entry	R ₁	R_2	R ₃	Product	Yield (%) ^a
1	Ph	Н	Н	3a	91
2	<i>t</i> -Bu	Н	Н	3b	94
3	<i>i</i> -Pr	Me	Me	3c	88
4	Et	Н	Me	3d	90
5	$(CH_2)_4$		Н	3e	87
6	(CH ₂) ₅		Н	3f	94
7	(CH ₂) ₇		Н	3g	83

^a Isolated yield based on acetal.

In conclusion, we have developed a convenient preparation of diethyl 3-bromo-3,3-difluoropropyl acetal (1) and studied the SnCl₄-promoted cross-coupling reaction of diethyl 3-bromo-3,3-difluoropropyl acetal with trimethylsilyl enol ethers, giving γ -bromodifluoromethyl- β -ethoxy ketones (3). Work continues in exploring further the use of 1 and 3 in the construction of various functionalized CF₂containing compounds.

3. Experimental

¹H NMR spectra were recorded on a 300, 90 or 60 MHz spectrometer with Me₄Si as internal standard. ¹⁹F NMR spectra were obtained on a 56.4 MHz spectrometer using trifluoroacetic acid as external standard, downfield shifts being designated as negative. All chemical shifts (δ) are expressed in ppm, coupling constants (*J*) are given in Hz. Mass spectra were obtained using EI ionization at 70 eV. The IR spectra were recorded on a Shimadzu IR-440 spectrometer. All reactions were routinely monitored with the aid of TLC or ¹⁹F NMR spectroscopy. Dichloromethane was freshly distilled from calcium hydride.

3.1. Diethyl 3-bromo-3,3-difluoropropanal diethyl acetal (1)

A mixture of CF_2Br_2 (31.5 g, 0.15 mol), ethyl vinyl ether (7.2 g, 0.1 mol), $Na_2S_2O_4$ (26.1 g, 0.15 mol) and $NaHCO_3$ (25.2 g, 0.3 mol) in ethanol (40 ml) was stirred at 60°C for 5 h. The reaction mixture was poured into water, and extracted with diethyl ether (3 × 20 ml). The combined extracts were washed with water, brine and dried over Na_2SO_4 . After evaporation of the solvent, the residue was distilled under reduced pressure to give **1** (20.0 g, 81%) as a colorless liquid; bp 64°C/4 mm Hg; $\delta_{\rm H}$ (CCl₄, 60 MHz) 4.8 (1H, t, J = 4.0 Hz), 3.4–3.5 (4H, m), 2.7 (2H, d-t, J = 14.0, 4.0 Hz), 1.2 (3H, t, J = 7.0 Hz); $\delta_{\rm F}$ (CCl₄) –35.6 (t, J = 14.0 Hz).

3.2. General procedure for $SnCl_4$ -promoted reaction of diethyl 3-bromo-3,3-difluoropropyl acetal (1) with trimethylsilyl enol ethers (2)

Stannic chloride (1.1 g, 1.2 mmol) was added to a well stirred solution of acetal 1 (1.0 g, 4 mmol) and trimethylsilyl enol ether (5 mmol) in anhydrous CH_2Cl_2 (15 ml) at $-78^{\circ}C$. After 4 h, the reaction was quenched by addition of saturated aqueous NaHCO₃ (10 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined extracts were washed with brine (50 ml), dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography on silica gel.

3.3. Spectroscopic data for 3a

Oil, IR (liquid film): 2980, 2687, 1598, 1450, 1374, 1203 cm⁻¹; $\delta_{\rm H}$ (CDCl₃, 300 MHz) 7.97–7.94 (2H, m), 7.62–7.56 (1H, m), 7.51–7.46 (2H, m), 4.39–4.32 (1H, m), 3.58 (2H, q, J = 7.0 Hz), 3.40 (1H, d-d, J = 16.8, 6.7 Hz), 3.08 (1H, d-d, J = 16.8, 5.7 Hz), 2.80–2.69 (2H, m), 1.13 (t, 3H, J = 7.0 Hz); $\delta_{\rm F}$ (CCl₄) –36.0 (t, J = 14.0 Hz); m/z (EI) 322/320 (M⁺, 44.73%), 292 (53.08), 290 (55.23), 276 (23.47), 275 (49.90), 105 (100); HRMS for C₁₃H₁₅F₂O₂Br⁷⁹: Calculated 320.0224; Found 320.0234.

3.4. Spectroscopic data for 3b

Oil, IR (liquid film): 2979, 1708, 1480, 1371, 1205, 1132 cm⁻¹; $\delta_{\rm H}$ (CDCl₃, 300 MHz) 4.20–4.16 (1H, m), 2.93 (1H, d-d, J = 17.2, 7.1 Hz), 2.69–2.49 (3H, m), 1.19–1.13 (12H, m); $\delta_{\rm F}$ (CCl₄) –36.6 (t, J = 14.0 Hz); m/z (EI) 302/300 (M⁺, 20.82%), 273 (11.89), 203 (85.43), 173 (26.85), 85 (23.75), 57 (100.00). Anal. Calc. for C₁₁H₁₉F₂O₂Br: C, 43.85; H, 6.31; F, 12.62. Found: C, 43.91; H, 6.57; F, 12.61%.

3.5. Spectroscopic data for 3c

Oil, IR (liquid film): 2978, 1702, 1472, 1207, 1108, 1006 cm⁻¹; $\delta_{\rm H}$ (CDCl₃, 300 MHz) 3.93–3.90 (1H, m), 3.72–3.67 (1H, m), 3.47–3.44 (1H, m), 3.13–3.08 (1H, m), 2.53–2.41 (2H, m), 1.27–1.00 (15H, m); $\delta_{\rm F}$ (CCl₄)

-36.0 (t, J = 14.0 Hz); m/z (EI) 316/314 (M⁺, 14.67%), 203 (22.90), 201 (24.22), 71 (100.00), 69 (10.00), 43 (57.95); HRMS for $C_{12}H_{21}F_2O_2Br^{79}$: Calculated 314.0694; Found 314.0708.

3.6. Spectroscopic data for 3d

Oil, IR (liquid film): 2980, 1716, 1461, 1377, 1192, 1021 cm⁻¹; $\delta_{\rm H}$ (CDCl₃, 300 MHz) 3.89–3.84 (1H, m), 3.59–3.53 (1H, m), 3.47–3.42 (1H, m), 2.89–2.85 (1H, m), 2.63–2.49 (4H, m), 1.27–1.00 (9H, m); $\delta_{\rm F}$ (CCl₄) (–35.3 (t, *J* = 14.0 Hz); m/z (EI) 286 (M⁺, 29.84%), 203 (25.85), 201 (26.75), 143 (11.97), 121 (9.61), 103 (13.50), (57, 100.00). Anal. Calc. for C₁₀H₁₇F₂O₂Br: C, 41.81; H, 5.92; F, 13.24. Found: C, 41.83; H, 6.06; F, 13.58%.

3.7. Spectroscopic data for 3e

Oil, IR (liquid film): 2976, 1455, 1375, 1204, 1157, 1126 cm⁻¹; $\delta_{\rm H}$ (CCl₄, 90 MHz) 4.10 (1H, m), 3.70–3.20 (2H, m), 2.80–1.60 (9H, m), 1.10 (3H, t, *J* = 7.0 Hz); $\delta_{\rm F}$ (CCl₄) -35.6 (t, *J* = 14.0 Hz); m/z (EI) 284 (M⁺, 39.76%), 239 (87.99), 201 (38.04), 159 (45.23), 141 (100.00), 121 (44.05). Anal. Calc. for C₁₀H₁₅F₂O₂Br: C, 42.11; H, 5.26. Found: C, 42.41; H, 5.40%.

3.8. Spectroscopic data for 3f

Oil, IR (liquid film): 2939, 1711, 1451, 1374, 1202, 1129 cm⁻¹; $\delta_{\rm H}$ (CDCl₃, 300 MHz) 4.12 (1H, d-t, J = 11.3, 5.3 Hz), 3.64–3.50 (2H, m), 2.67–1.60 (11H, m), 1.13 (3H, t, J = 7.0 Hz); $\delta_{\rm F}$ (CCl₄) –36.6 (t, J = 14.0 Hz); m/z (EI) 299 (M⁺, 100.00%), 203 (68.88), 201 (69.55), 155 (94.43), 121 (44.05). Anal. Calc for C₁₁H₁₇F₂O₂Br: C, 44.15; H, 5.69; F, 12.71. Found: C, 44.12; H, 5.91; F, 12.83%.

3.9. Spectroscopic data for 3g

Oil, IR (liquid film): 2932, 1699, 1456, 1375, 1191, 1106 cm⁻¹; $\delta_{\rm H}$ (CCl₄, 90 MHz) 4.16–3.90 (1H, m), 3.80–3.60 (2H, q, J = 7.0 Hz), 2.80–2.20 (3H, m), 2.15–1.30 (10H, m), 1.26–1.03 (3H, m); $\delta_{\rm F}$ (CCl₄) –37.3 (t, J = 14.0 Hz); m/z (EI) 313 (M⁺, 93.26%), 269 (73.88), 203 (74.05), 121 (100), 112 (81.42), 95 (90.18). Anal. Calc. for C₁₂H₁₉F₂O₂Br: C, 46.01; H, 6.07. Found: C, 45.97; H, 6.17%.

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