

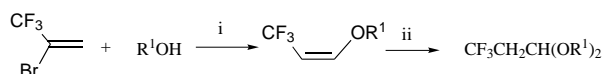
TiCl₄-promoted cross-coupling reaction of dialkyl 3,3,3-trifluoropropyl acetals for the preparation of CF₃-containing functionalized compounds

Feng Hong^{*,†} and Chang-Ming Hu^{*}

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, PR China

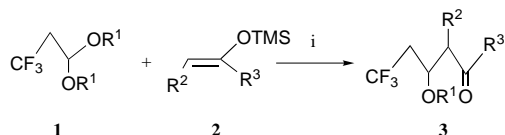
The TiCl₄-promoted reaction of dialkyl 3,3,3-trifluoropropyl acetals with trimethylsilyl enol ethers to give γ -trifluoromethyl- β -alkoxy ketones is described.

Trifluoromethylated compounds have proved to be very useful as medicinal compounds, pesticides and materials due to the unique lipophilic character of the trifluoromethyl group which is also isosteric and isoelectronic with a methyl group.¹ Great efforts have been made to develop useful methods for the introduction of the CF₃ group into organic compounds.² The building block approach, known for its high selectivity, good yields and simplicity, has been demonstrated to be a practical and powerful tool.³ However, the invention of more CF₃-containing building blocks, aimed at preparing various compounds with other desired functional groups, is still highly desirable. α -CF₃ Alcohols, for example, can be easily prepared through the reaction of TMSCF₃ with ketones and aldehydes.⁴ β -CF₃ Alcohols could presumably be made by the reaction of an organometallic reagent derived from 2,2,2-trifluoroethyl bromide or iodide with ketones and aldehydes. However, the arduous preparation of 2,2,2-trifluoroethyl bromide or iodide⁵ and the unavoidable β -elimination of fluoride from their derived organometallic reagents would prohibit such a route being practically feasible. We recently reported a novel and convenient preparation of (*Z*)-3,3,3-trifluoropropenyl ethers and their transformation into CF₃-substituted propyl acetals (Scheme 1).⁶ Based on the



Scheme 1 Reagents and conditions: i, KOH, 86–96%; ii, R¹OH, cat. PTSA, CH₂Cl₂, 90–97%

extensively studied reactivities of acetals,⁷ we envisaged that these CF₃-substituted acetals could be used as new CF₃-containing building blocks. Herein, we describe the TiCl₄-promoted reaction of these acetals with trimethylsilyl enol ethers to give γ -trifluoromethyl- β -alkoxy ketones which can be used as precursors of β -CF₃ alcohols (Scheme 2).



Scheme 2 Reagents and conditions: i, TiCl₄, CH₂Cl₂, -78 °C, 63–85%

The results are listed in Table 1. The reaction succeeds not only with the dimethyl acetal **1a** but also with the diisobutyl acetal **1d**, albeit in reduced yield for the latter. The stereo-

Table 1 Synthesis of γ -trifluoromethyl- β -alkoxy ketones^a

Entry	Acetal 1	Silyl enol ether 2	t/h	Product 3	Yield (%) ^b
	R ¹	R ²	R ³		
1	Me 1a	H	Ph	2a 4	3a 85
2	Me 1a	H	Bu ^t	2b 5	3b 73
3	Me 1a	-(CH ₂) ₄ -		2c 6	3c 67
4	Et 1b	H	Ph	2a 4	3d 82
5	Et 1b	H	Bu ^t	2b 5	3e 76
6	Et 1b	-(CH ₂) ₄ -		2c 7	3f 63
7	Bu ⁿ 1c	H	Bu ^t	2b 7	3g 67
8	Bu ^t 1d	H	Bu ^t	2b 7	3h 65

^a All reactions were performed in CH₂Cl₂ under nitrogen on a 10 mmol scale for **1** and **2** using 1.1 equiv. of TiCl₄. ^b Yields of isolated product.

selectivity of products **3c** and **3f** was not determined. Purely to demonstrate their utility as CF₃-containing building blocks, only homoacetals were used in these reactions in order to simplify the characterization of the products. However heteroacetals are also readily available following the same preparation.⁶ Dimethyl 3,3,3-trifluoropropyl acetal gave γ -trifluoromethyl β -methoxy ketones which are likely to be transformed into β -CF₃ alcohols by demethylation using TMSI.⁸

In conclusion, we have studied the TiCl₄-promoted reaction of dialkyl 3,3,3-trifluoropropyl acetals with trimethylsilyl enol ethers, giving γ -trifluoromethyl β -methoxy ketones. The products obtained using dimethyl 3,3,3-trifluoropropyl acetals can be conveniently converted to β -CF₃ alcohols following the literature method, thus providing a way of making such compounds.

Experimental

Typical procedure for TiCl₄-promoted reaction of dialkyl 3,3,3-trifluoropropyl acetals with silyl enol ethers

To a solution of TiCl₄ (2.1 g, 11.2 mmol) in anhydrous CH₂Cl₂ (15 ml) was added **1b** (2.0 g, 10.8 mmol) dropwise at -78 °C under nitrogen with stirring. Silyl enol ether **2a** (2.0 g, 10.8 mmol) was quickly introduced into the flask and stirring was continued for 4 h at the same temperature. The reaction mixture was poured into H₂O (40 ml) and extracted with diethyl ether (2 × 40 ml). The combined extracts were washed with saturated aqueous NaHCO₃ (40 ml), brine (50 ml), dried (Na₂SO₄) and concentrated. Distillation under reduced pressure gave **3b** (2.3 g, 82%) as a colourless oil; bp 92–94 °C/0.4 mmHg; ν_{\max} (neat)/cm⁻¹ 1680 (C=O), 1120 (C-F), 1030 (C-O); δ_{H} (60 MHz, CDCl₃, J/Hz) 1.15 (3 H, t, *J* 6, CH₃), 2.35–2.58 (2 H, m, CH₂CF₃), 3.1 (1 H, dd, *J* 16 and 6, 1 × CH₂CO), 3.4 (1 H, dd, *J* 16 and 6, 1 × CH₂CO), 3.60 (2 H, q, *J* 6, CH₂O), 4.25–4.40 (1 H, m, CHO), 7.40–8.0 (5 H, m, ArH); δ_{C} (60 MHz, CDCl₃) -14.5 (s), (CF₃CO₂H was used as standard for 0 ppm); *m/z* 261 (M + H)⁺ (Found: C, 60.09; H, 5.38; F, 21.96. C₁₃H₁₅F₃O₂ requires C, 60.00; H, 5.77, 21.90%).

[†] Current address: Research Department, Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224, USA.

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