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Expedient synthesis of α,α -difluorohomopropargylic alcohols from TIPS-difluorobromopropyne via a Zn-mediated propargylation of aldehydes and ketones

ZhiGang Wang and Gerald B. Hammond*

Department of Chemistry and Biochemistry, The University of Massachusetts Dartmouth, North Dartmouth, Massachusetts 02747, USA

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Abstract

The synthesis of α,α -difluorohomopropargyl alcohols containing an alkynyl silane moiety is reported. The title compound was prepared by the reaction of the organozinc derivative of TIPS-bromodifluoropropyne with aldehydes or ketones under mild conditions and in good yields. © 2000 Elsevier Science Ltd. All rights reserved.

The search for new methods for the introduction of the CF_2 group in organic molecules is an area of much current interest.¹ The unique stereoelectronic properties of the *gem*-difluoromethylene group, in which the CF_2 carbon is sp^3 hybridized, have fostered its widespread utilization in pharmacologically active substances. For example, the presence of a CF_2 has aided in the formation of stable hydrates and hemiketals capable of inhibiting proteases and esterases;² CF_2 has been employed as an isoelectronic–isosteric replacement for the oxygen atom in phosphate analogues;³ and in the synthesis of β,β -difluoro- α -amino acids,⁴ and fluorinated arachidonic acid,⁵ among other uses.

As part of our ongoing research on fluorinated building blocks, we speculated that TIPS- α,α -difluorohomopropargyl alcohol **2**, could be an efficient conduit for fluorine incorporation in an organic compound. Compound **2** is equipped with two synthetic handles on both ends of the CF_2 group: an alkynyl silane and a hydroxyl group. To our knowledge, the only reported⁶ synthesis of α,α -difluoropropargylic alcohols was provided by Kobayashi et al.,⁷ who used zinc activated with HgCl_2 in the reaction of aryl- or alkyl-substituted bromodifluoroacetylenes with aldehydes ($\text{R}_2=\text{H}$) to give α,α -difluoropropargylic alcohols. Kobayashi obtained his bromodifluoroacetylenes following Wakselman's procedure,⁸ in disappointingly low yields by the reaction of an alkyl- or aryl-substituted acetylene with CF_2Br_2 , under strongly basic conditions.

Our strategy for the preparation of **2** makes use of a highly efficient synthesis of TIPS-bromodifluoropropyne **1**, recently discovered in our laboratory.⁹ Compound **1** was assembled in

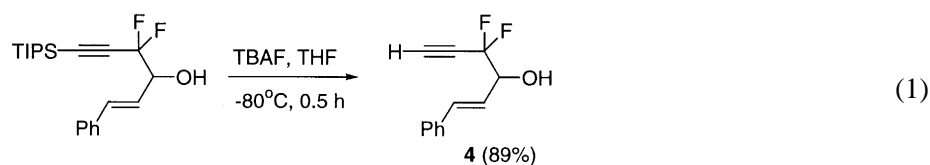
* Corresponding author. Tel: 508-999-8865; fax: 508-910-6918; e-mail: ghammond@umassd.edu (G. B. Hammond)

one step (92% GC–MS, 81% isolated) by the reaction of CF_2Br_2 with lithium TIPS-acetylide. We attributed the success of this reaction to the presence of the TIPS group, which possesses remarkably different properties compared to other alkylsilyl groups.¹⁰ Treatment of **1** with zinc at room temperature using Methods A or B forms an organozinc intermediate capable of reacting with a wide variety of aldehydes and ketones at room temperature to give the desired α,α -difluorohomopropargylic alcohol **2** in good yield (see Table 1). Aldehydes, being more electrophilic than ketones, furnished the corresponding alcohols in higher yields. Method B provided a higher yield of **2** because the organozinc intermediate could be trapped by the aldehyde as soon as it was formed. Dimer **3** is the only observable by-product of this reaction and was easily removed during chromatography due to its very low polarity. The ratio of **2**:**3** ranged from approximately 3:1 to 5:1.

Method A (two-step procedure): To a solution of **1** (824 mg, 2.3 mmol) in THF (7 mL) was added zinc dust (208 mg, 1.2 equiv.). The mixture was sonicated for 10 min and stirred at room temperature until the absence of starting material was observed (about 1 h). 2-Octynal (389 μL , 1.0 equiv.) was added and the resulting mixture was stirred for 20 h. Solvent removal, standard work-up (saturated NH_4Cl , ethyl acetate extraction) and purification (silica gel flash chromatography), furnished **2** (entry 4).¹¹

Method B (one-step procedure): To a solution of **1** (907 mg, 2.91 mmol) and 3-methyl-2-butenal (290 μL , 1.0 equiv.) in THF (10 mL) was added zinc dust (229 mg, 1.2 equiv.). The mixture was sonicated for 15 min and stirred at room temperature for 18 h. Standard work-up followed by flash chromatography gave **2** (entry 2).¹²

When needed, the TIPS-protecting group in **2** can be easily removed, as demonstrated by the conversion of **2** (entry 7) to **4** (Eq. (1)) under mild conditions and in excellent yield. This result will allow an easy access to other propargylic, and possibly allylic α,α -difluorocarbonyl compounds, after oxidation of the alcohol and hydrogenation of the triple bond.



Other organometallic applications of **1** to the synthesis of organofluoro compounds are under investigation.

Acknowledgements

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Table 1

entry	R ₁	R ₂	2	yield % ^a	¹⁹ F NMR ^c
1	Ph	H		60	δ -92.48, -94.62 ² J _{FF} =275 Hz
2	(H ₃ C) ₂ C=CH	H		57 ^b	δ -94.23, -97.92 ² J _{FF} =273 Hz
3	CH ₃ (CH ₂) ₅	H		51	δ -94.82, -97.35 ² J _{FF} =276 Hz
4	H ₃ C(H ₂ C) ₄ C≡C	H		54	δ -94.07, -97.22 ² J _{FF} =270 Hz
5		H		62 ^b	δ -89.70, -92.06 ² J _{FF} =279 Hz
6	<i>trans</i> H ₃ CHC=CH	H		64 ^b	δ -94.68, -97.45 ² J _{FF} =274 Hz
7	<i>trans</i> -PhHC=CH	H		70 ^b	δ -94.30, -96.65 ² J _{FF} =274 Hz
8	Me	Me		43	δ -99.70
9	Me	Et		42	δ -98.04, -99.11 ² J _{FF} =272 Hz
10	Me	CH=CH ₂		39	δ -97.76, -98.97 ² J _{FF} =271 Hz
11		-(CH ₂) ₄ -		52	δ -97.13
12		-(CH ₂) ₅ -		48	δ -101.01
13	Ph	Me		41	δ -94.48, -96.69 ² J _{FF} =271 Hz
14	Ph	Ph	No Reaction	--	

^a Yields are based on TIPS-difluorobromopropyne and determined by GC-MS analysis of the crude product. ^b Method B was employed. ^c Solvent CDCl₃, reference CFCl₃

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11. ^1H NMR δ 4.54 (m, 1H), 2.21 (dt, 2H, $^3J_{\text{HH}}=7.1$ Hz, $^5J_{\text{HH}}=2.0$ Hz), 2.04 (s, 1H), 1.52–1.26 (m, 6H), 1.12 (s, 21H), 0.90 (t, 3H, $^3J_{\text{HH}}=7.1$ Hz). ^{13}C NMR δ 111.57 (t, $^1J_{\text{FC}}=239$ Hz), 96.08 (t, $^2J_{\text{FC}}=37$ Hz), 93.02 (t, $^3J_{\text{FC}}=6$ Hz), 89.03, 74.03 (t, $^3J_{\text{FC}}=4$ Hz), 66.52 (t, $^2J_{\text{FC}}=33$ Hz), 30.99, 27.89, 22.13, 18.66, 18.07, 14.00, 10.88. EI-MS *m/e* 355 (M^+ , 3), 304 (12), 261 (2), 241 (15), 157 (17), 109 (18), 77 (100). Anal. calcd for $\text{C}_{20}\text{H}_{34}\text{SiF}_2\text{O}$: C, 68.13; H, 9.64. Found: C, 68.08; H, 9.74.
12. ^1H NMR δ 5.30 (m, 1H, $^4J_{\text{FH}}=9.0$ Hz), 4.56 (m, 1H, $^3J_{\text{FH}}=11.6$ Hz, $^3J_{\text{FH}}=8.9$ Hz, $^3J_{\text{HH}}=6.4$ Hz), 2.05 (s, 1H), 1.79 (d, 3H, $^4J_{\text{HH}}=1.4$ Hz), 1.76 (d, 3H, $^4J_{\text{HH}}=1.3$ Hz), 1.09 (s, 21H). ^{13}C NMR δ 141.6, 119.2 (t, $^3J_{\text{FC}}=2$ Hz), 113.2 (t, $^1J_{\text{FC}}=238$ Hz), 96.9 (t, $^2J_{\text{FC}}=38$ Hz), 92.44 (t, $^3J_{\text{FC}}=6$ Hz), 71.3 (t, $^2J_{\text{FC}}=30$ Hz, $^2J_{\text{FC}}=27$ Hz), 26.00, 18.73, 18.38, 10.87. EI-MS *m/e* 273 ($\text{M}^+ - 43$, 3), 253 (4), 203 (3), 169 (8), 131 (4), 105 (20), 85 (100).