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A one-pot synthesis of conjugated fluoroenynes via 2,2-difluorovinylcopper intermediates

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Abstract

1,1-Difluoro-1,3-enynes have been synthesized in good yield via the *in-situ* generation of 1-alkyl-2,2-difluorovinylboranes by successive treatment of 2,2,2-trifluoroethyl *p*-toluenesulfonate with butyl-lithium and trialkylboranes, followed by the coupling reaction with 1-halo-1-alkynes in the presence of cuprous iodide.

Introduction

Conjugated enynes are versatile intermediates in the synthesis of a wide range of compounds with a complex structure, including natural products [1]. The increasing availability of enynes has made them additionally attractive as useful functionalized building blocks [2]. By contrast, there have been only a limited number of methods for the preparation of fluorinated enynes in spite of their great utility in the synthesis of selectively fluorinated compounds [3–6], which have received much attention in a variety of fields such as medicinal and biological chemistry and material science. Moreover, to our knowledge, all of the methods with one exception [3] were based on the palladium-catalyzed coupling reactions of 1-alkynes or 1-alkynylzinc reagents with fluorinated 1-halo-1-alkenes, whose prior preparation was required [4–6]. We wish to report herein a new approach to difluoroenynes using a readily available 2,2,2-trifluoroethanol derivative.

Results and discussion

We have recently developed a novel method for the *in-situ* generation of fluorinated vinylcopper reagents **4** from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**) [7]. This method consists of (i) the formation of difluorovinyl boranes (**3**) by successive treatment of **1** with butyl-lithium and trialkylboranes and (ii) the transmetalation of **3** with cuprous iodide. The *non-fluorinated*

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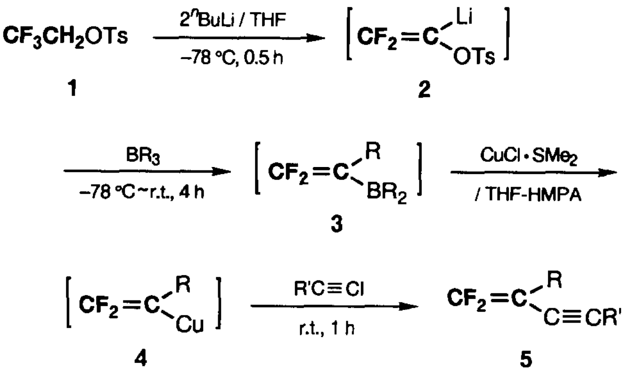
counterparts of **4**, 1-alkenylcopper reagents, are well known to couple with 1-halo-1-alkynes under mild conditions, providing easy access to conjugated enynes [8]. These facts prompted us to explore the use of intermediary 2,2-difluorovinylcopper (**4**) in the coupling reaction with 1-halo-1-alkynes. Thus, a one-pot synthesis of 1,1-difluoro-1,3-enynes (**5**) from **1** was achieved via the successive alkylation and alkynylation of the *difluorovinylidene* unit ($F_2C{=}C$) mediated by boron and copper, respectively (Scheme 1).

The coupling reaction was attempted between *in-situ* generated dibutyl(1-butyl-2,2-difluorovinyl)borane (**3a**; $R = Bu^n$) and 1-halo-1-alkynes in the presence of 1 equiv. of cuprous iodide. Employing 1-iodo-4-phenyl-1-butyne as a 1-halo-1-alkyne led to the desired 1,3-enyne **5a** ($R = Bu^n$, $R' = (CH_2)_2Ph$) in 53% yield, which was better than the 40% yield of the corresponding alkynyl bromide. The dimeric diyne was also produced as a by-product presumably via metal–halogen exchange, followed by decomposition of the resulting 1-alkynylcopper. The formation of self-coupling products (conjugated diynes) was a major problem in this type of reaction [8]. Since metal salts seemed to hold the key for suppressing the self-coupling reaction, screening on copper(I) salts was attempted. We finally found that dimethyl sulfide complexes of cuprous chloride and bromide [9] were effective in promoting the cross-coupling reaction and the yields of **5a** were raised to 76% and 73%, respectively.

Several other trialkylboranes and alkynyl iodides were examined in the above reaction by the use of $CuCl \cdot SMe_2$ as a copper(I) salt. The corresponding 1,1-difluoro-1,3-enynes with various carbon substituents were obtained in good yields as summarized in Table 1.

The coupling reaction with iodoethynylsilane afforded the difluoroenynes bearing a silyl group on the acetylenic carbon **5** ($R' = SiMe_3$; Table 1, Entries 5–7). The cleavage of the Si–C bond in these silylacetylenes was attempted in order to liberate terminal acetylenes. In our initial attempt at desilylation, **5b** [$R = (CH_2)_4Ph$, $R' = SiMe_3$] was treated with potassium carbonate in methanol [10]. The reaction caused the decomposition of **5b**, apparently due to its high reactivity at the difluoromethylene carbon toward nucleophiles because



Scheme 1.

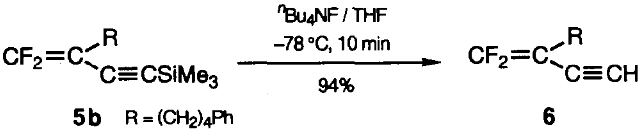
TABLE 1

One-pot synthesis of 1,1-difluoro-1,3-enynes (**5**)[a]

Entry	R	R′	Yield (%)[b]
1	Bu^n	$Ph(CH_2)_2$	76 (**5a**)
2		$Me(CH_2)_4$	77
3		c-Hex	77
4		Ph	65
5		Me_3Si	66
6		Bu^tMe_2Si	77
7	$Ph(CH_2)_4$	Me_3Si	60 (**5b**)
8	Bu^s	$Ph(CH_2)_2$	64

[a] Unless otherwise noted, all reactions were carried out under the conditions described in the text. Molar ratio of **1**:BR_3:1-halo-1-alkyne = 1:1.1:0.9.

[b] Isolated yield. All compounds were fully characterized by ^1H NMR, ^{19}F NMR, ^{13}C NMR, IR and mass spectra.



Scheme 2.

of the double activation by fluorine atoms and an alkynyl group. Based on this consideration, we tried treatment with tetrabutylammonium fluoride at a low temperature over a short period (−78 °C, 10 min), which promoted the desired desilylation to give only the enyne with a terminal acetylene **6** [R = $(CH_2)_4Ph$] in excellent yield (Scheme 2). Terminal enynes occur in many natural products and are widely utilized in organic synthesis [1]. These facts should also make this method a valuable entry to fluorinated enynes.

It should be noted that the 1,1-difluoro-1,3-enynes reported here possess not only a rarely precedented substitution pattern of fluorine on a conjugated enyne system*, but a high reactivity toward nucleophiles as mentioned above which permits the introduction of a carbon unit by the substitution of a fluorine atom via an addition–elimination process. This substitution and the polymerization of fluoroenynes leading to fluorine-containing polyacetylenes will be described in due course.

Experimental

A typical reaction procedure is described for the synthesis of **5b**. To compound **1** (98 mg, 0.39 mmol) in THF (2.5 ml) was added butyl-lithium

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*To date, only one 1,1-difluoro-1,3-enyne, i.e. 1,1-difluoro-1-decen-3-yne (**5**; R = H, R′ = n-Hex), has been synthesized and reported [4].

(0.53 ml, 1.52 M in hexane, 0.81 mmol) at −78 °C over 10 min under a nitrogen atmosphere. The reaction mixture was stirred for 30 min at −78 °C to generate 2,2-difluoro-1-tosyloxyvinyl-lithium (**2**), and then treated at −78 °C with tris(4-phenylbutyl)borane, generated from 4-phenylbutene (168 mg, 1.27 mmol) and a borane–THF complex (0.42 ml, 1.0 M in THF, 0.42 mmol). After being stirred for 1 h at −78 °C, the mixture was warmed to room temperature and stirred for an additional 3 h. To the resulting solution of vinylborane were added successively hexamethylphosphoric triamide (HMPA, 0.9 ml), iodoethynyltrimethylsilane (78 mg, 0.35 mmol) and cuprous chloride/dimethyl sulfide (1:1) (62 mg, 0.38 mmol) [9]. After the mixture had been stirred for 1 h at room temperature, water was added to quench the reaction. Usual work-up followed by column chromatography on silica gel (hexane) gave **5b** (61 mg, 60%) as a colorless liquid.

1,1-Difluoro-2-(4-phenylbutyl)-4-trimethylsilyl-1-buten-3-yne (**5b**) (nc): IR (neat) (cm^{-1}): 2940; 2860; 2170; 1715; 1300; 1250; 1230; 1100; 860; and 700. ^{1}H NMR ($CDCl_3$) δ: 0.22 (9H, s); 1.36–1.89 (4H, m); 1.89–2.40 (2H, m); 2.66 (2H, m); and 7.21 (5H, br s) ppm. ^{19}F NMR ($CDCl_3/C_6F_6$) δ: 76.9 (1F, d, J(F–F) = 17 Hz); and 82.4 (1F, d, J(F–F) = 17 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 0.0, 26.7, 27.2 (t, J(C–F) = 2 Hz); 30.5, 35.7, 78.7 (dd, J(C–F) = 34 Hz, 15 Hz); 96.7 (dd, J(C–F) = 8 Hz, 4 Hz); 99.3 (t, J(C–F) = 5 Hz); 125.8, 128.4, 128.5, 142.4 and 159.6 (dd, J(C–F) = 296 Hz, 292 Hz) ppm. MS (70 eV) *m/z*: 292 (M$^+$); 218; 165; 91 (base peak); and 77. Found: *m/z*, 292.1469. Calc. for $C_{17}H_{22}F_2Si$: M, 292.1457.

1,1-Difluoro-2-(4-phenylbutyl)-1-buten-3-yne (**6**) (nc): Compound **5b** (90 mg, 0.31 mmol) in THF (2 ml) was treated with tetrabutylammonium fluoride (0.46 ml, 1.0 M in THF, 0.46 mmol) at −78 °C for 10 min. After usual work-up followed by thin-layer chromatography on silica gel (hexane), **6** (64 mg, 94%) was obtained as a colorless liquid. IR (neat) (cm^{-1}): 3270; 2910; 1715; 1600; 1495; 1450; 1295; 1145; 1095; and 695. ^{1}H NMR ($CDCl_3$) δ: 1.32–1.84 (4H, m); 1.84–2.28 (2H, m); 2.36–2.80 (2H, m); 2.94 (1H, dd, J(H–F) = 2.2 Hz, 1.2 Hz); and 7.18 (5H, br s) ppm. ^{19}F NMR ($CDCl_3/C_6F_6$) δ: 77.5 (1F, d, J(F–F) = 17 Hz); and 82.0 (1F, d, J(F–F) = 17 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 26.5, 27.1 (t, J(C–F) = 2 Hz); 30.4, 35.6, 75.7 (dd, J(C–F) = 9 Hz, 4 Hz); 77.5 (dd, J(C–F) = 35 Hz, 15 Hz); 81.7 (t, J(C–F) = 6 Hz); 125.7, 128.3, 128.4, 142.3 and 159.8 (dd, J(C–F) = 296 Hz, 292 Hz) ppm. MS (70 eV) *m/z*: 220 (M$^+$); 149; 117; 105; 91 (base peak); and 57. Found: *m/z*, 220.1087. Calc. for $C_{14}H_{14}F_2$: M, 220.1063.

Acknowledgments

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