Facile Preparation of CF_3-Containing 1-Bromoallenes

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Received 17 September 2009

Abstract: The novel synthetic method is described for preparation of not only 1-bromo- but 1,3-dibromo-1-trifluoromethylated allenes from the corresponding propargylic alcohols with a combination of CBr_4 and Ph_3P. Selection of the organic solvent employed enabled us to access to these two different allenes quite readily.

Key words: alkynes, allenes, fluorine, trifluoromethyl, bromination

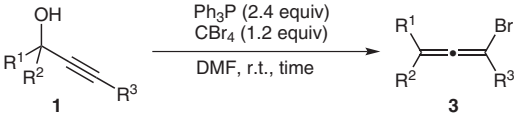
Currently, organofluorine compounds have attracted an enormous interest because of their remarkable properties on the basis of the special electronic character of fluorine which has contributed to their wide application to novel pharmaceuticals, advanced materials, and so on.[1] We have recently demonstrated the transformation of propargylic alcohols **1** into 3-mono- and 3,3-disubstituted allenes with a CF_3 group at the 1-position, $CF_3CH{=}C{=}CR^1R^2$.[2a] Allenes have been recognized as attractive and useful organic compounds and utilized as a variety of synthetic building blocks or convenient intermediates.[3] Such materials are also found in nature and panacene, isolated in 1977, is known as one of the representative allenes containing a bromine atom.[4] While nonfluorinated allenes enjoy both utilization and wide application, there have been only limited synthetic pathways for fluorinated counterparts,[2i–2k] especially the ones with a CF_3 group.[2b–2h] In this paper, we present the facile and straightforward conversion of the corresponding propargylic alcohols **1** into trifluoromethylated bromoallenes **3** by treatment with CBr_4 and Ph_3P.[5]

The combined reagent system CX_4–Ph_3P (X = Cl or Br) has been employed for halogenation of primary and secondary hydroxyl groups under mild conditions which usually proceeds in an S_N2 manner.[6] When we applied this method to the alcohol **1a**, unexpected transformation to the bromoallene **3a** was observed along with formation of a small amount of the corresponding 'normal product', propargylic bromide **2a**.

Brief investigation of the reaction conditions led to conclusion that Ph_3P and CBr_4 in DMF at ambient temperature were appropriate for the preparation of allenes with such substituents as a trifluoromethyl group and bromine at the geminal site and thus, we next examined generalization of this reaction (Table 1). It is interesting to note that this halogenation of the alcohol **1a** in other solvents (THF, Et_2O) afforded the bromoallene **3a** only sluggishly, but instead, the propargylic bromide **2a** and the 1,3-dibromoallene **4a** in moderate and irreproducible yields, respectively. This CBr_4–Ph_3P reagent system was successfully applied to a variety of CF_3-containing propargylic alcohols **1a–j** in DMF at room temperature. Although various types of arene-substituted alcohols **1a–e** were converted into allenes **3a–e** in high yields (Table 1, entries 1–5), **3e** was the exception which could not be isolated due to its instability towards silica gel at the purification stage (entry 5).

The aliphatic alcohols **1f–h** were also transformed to **3f–h** successfully (entries 6–8), while the tertiary alcohols

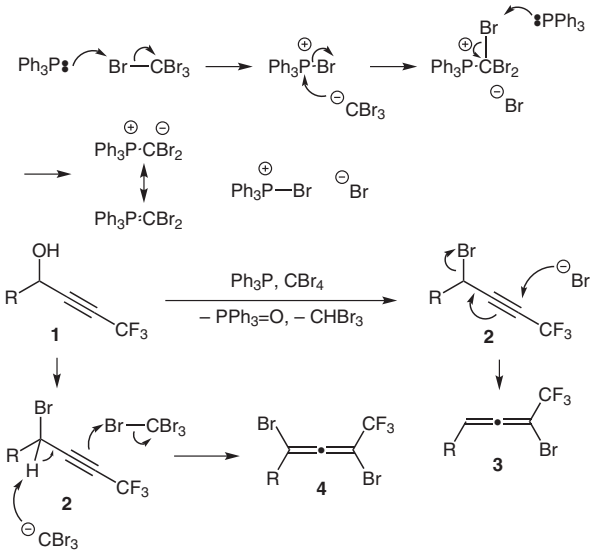
Table 1 Transformation of **1** into **3**



Entry	R^1	R^2	R^3	Time (h)	**3**	Yield (%)[a]
1	Ph	H	CF_3	2	**3a**[8]	85
2	1-Naphthyl	H	CF_3	2	**3b**	93
3	4-$MeOC_6H_4$	H	CF_3	2	**3c**	74
4	4-BrC_6H_4	H	CF_3	4	**3d**	85
5	2-furyl	H	CF_3	6	**3e**	67[b]
6	(*E*)-PhCH=CH	H	CF_3	24	**3f**	63
7	$PhCH_2CH_2$	H	CF_3	14	**3g**	89
8	*c*-Hex	H	CF_3	14	**3h**	87
9[c]	Ph	Me	CF_3	55	**3i**	39
10	$-(CH_2)_5-$		CF_3	90	**3j**	39
11	Ph	H	*n*-Bu	4	**3k**	86
12	$PhCH_2CH_2$	H	*n*-Bu	18	**3l**	0 (44)[d]
13	Ph	H	Ph	8	**3m**	–[e]

[a] Isolated yield.
[b] ^{19}F NMR yield determined by $PhCF_3$ as an internal standard.
[c] Ph_3P (4.8 equiv) and CBr_4 (2.4 equiv) were used.
[d] The value in the parenthesis was the yield of the corresponding propargylic bromide **2l**.
[e] A complex mixture was obtained.

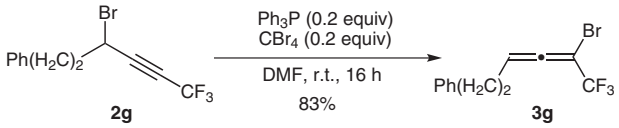
SYNLETT 2009, No. 20, pp 3352–3354
Advanced online publication: 18.11.2009
DOI: 10.1055/s-0029-1218383; Art ID: U09409ST



Scheme 1 Proposed mechanism for the conversion of **1** into bromoallenes **3** and **4**

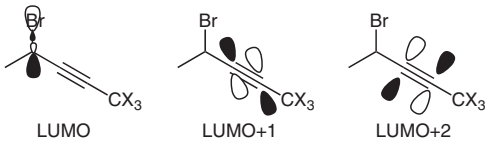
1i,j afforded the corresponding products only in low yields probably because of their increased steric hindrance around the site where the first S_N2-type attack was occurred (entries 9 and 10). Among nonfluorinated alcohols used, only **1k** recorded successful conversion into **3k** in an excellent yield which clearly demonstrated requirement of appropriate activation of substrates for this reaction.

The reaction mechanism is proposed as illustrated in Scheme 1. At first, usual CBr_4–Ph_3P-promoted halogenation of alcohols **1** would proceed to form propargylic bromides **2** whose further bromination in an S_N2' fashion led to ready formation of bromoallenes **3** (Scheme 1). Excellent conversion of the independently prepared propargylic bromide **2g** into the corresponding allene **3g** with a catalytic amount of the bromide source clearly supported this mechanism (Equation 1).



Equation 1 Isomerization of propargylic bromide **2g** to the corresponding allene **3g**

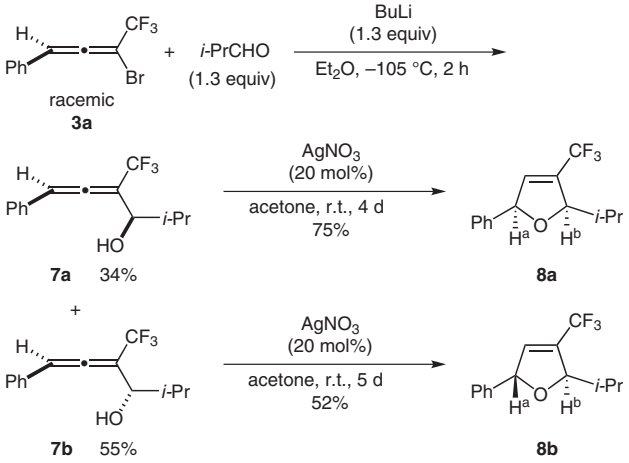
We performed DFT calculation of the model compound **6** for obtaining MO information along with its nonfluorinated prototype **5**. According to the result, compound **6** revealed the significantly lower energy levels of LUMO than **5**, and the similar tendency was also noticed for LUMO+1 and LUMO+2 (the depicted lobes are almost perpendicular and parallel to the C–Br bond, respectively) while the gap became smaller. These discrepancies would clearly demonstrated higher electrophilicity of **6** relative to **5** (Figure 1) and would be the primary reason why the second attack of bromide ion was occurred smoothly only in the case of trifluorinated substrates.



X	Compound	Energy level (eV) LUMO	LUMO+1	LUMO+2
H	**5**	–0.617	–0.356	–0.040
F	**6**	–2.021	–0.869	–0.367

Figure 1 Computation of **5** and **6** by Gaussian 03W using the B3LYP/6-311++G** level of theory

In order to examine the synthetic utility of **3** thus obtained, we further attempted the reaction with isobutyraldehyde after conversion into the corresponding allenyllithium, generated in situ by lithium–bromine exchange using butyllithium and the bromoallene **3a**. The desired allenylcarbinols **7a** and **7b**,[9] were readily obtained as a separable diastereomer mixture and isolated in 34% and 55% yields, respectively, after separation by silica gel column chromatography (Scheme 2).



Scheme 2 Preparation of dihydrofurans **8a** and **8b**

Relative stereochemistry of the minor adduct **7a** was determined by ^{1}H NMR analysis after stereospecific conversion into the corresponding diastereomerically pure 2,5-dihydrofuran **8a**[10] by treatment with 20 mol% $AgNO_3$ at room temperature for 4 days (Scheme 2).[7] The clear correlation between H^a and H^b was observed only in the NOESY spectrum of **8a**, not in the one of **8b**, which unambiguously proved the 2,5-*cis* stereochemical relationship of the former compound. Considering the Lewis acidic role of $AgNO_3$, this information also led to strong anticipation of the three dimensional structure of **7a** and **7b** as shown in Scheme 2.

In conclusion, we have demonstrated that CF_3-containing bromoallenes **3** were produced in high yields directly from alcohols **1** by way of the CBr_4–Ph_3P-mediated sequential bromination reactions. It was also appeared that this method was applicable to the nonfluorinated propargylic alcohol **1k** with adequate activating substituents. Allenyllithium derived from the bromoallene **3a** as the

representative example was conveniently transformed into the carbonyl adducts **7a** and **7b** in excellent yield. Further studies on expanding the scope of the substrates are in progress.

Acknowledgment

The authors are grateful to Tosoh F–Tech, Inc. for the generous gift of 2-bromo-3,3,3-trifluoropropene.

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(8) **Typical Procedure for the Preparation of the Bromoallene 3a**
To a solution of **1a** (0.12 g, 0.60 mmol) and Ph_3P (0.38 g, 1.4 mmol) in DMF (2.0 mL) was added CBr_4 (0.24 g, 0.72 mmol) at r.t. The solution was stirred at that temperature for 2 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with hexane–EtOAc (1:1, 3 × 15 mL). Concentration by rotary evaporator after dried over Na_2SO_4 furnished a crude mixture that was purified by silica gel chromatography (hexane–EtOAc, 20:1) to afford **3a** (0.14 g, 0.51 mmol, 85%) as a pale yellow oil. R_f = 0.79 (CH_2Cl_2–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.71 (q, *J* = 2.7 Hz, 1 H), 7.34–7.44 (m, 5 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 82.5 (q, *J* = 45.3 Hz), 106.8, 119.8 (q, *J* = 271.7 Hz), 128.5, 129.2, 129.4, 129.9, 202.6 (q, *J* = 3.1 Hz). ^{19}F NMR (283 MHz, $CDCl_3$): δ = –65.66 (s). IR (neat): 613, 653, 690, 720, 749, 819, 847, 897, 918, 951, 1003, 1029, 1045, 1075, 1119, 1267, 1293, 1313, 1397, 1459, 1496, 1597, 1736, 3034, 3066 cm^{-1}. HRMS–FAB: *m/z* calcd for $C_{10}H_7F_3Br$ [M + H]$^+$: 262.9683; found: 262.9668.

(9) **Procedure for the Preparation of the Allenylcarbinols 7a and 7b**
To a solution of **3a** (0.32 g, 1.20 mmol) and isobutyraldehyde (142 μL, 1.6 mmol) in Et_2O (5 mL) was added BuLi (0.98 mL, 1.6 mmol, 1.6 M in hexane) at –105 °C. The solution was stirred at that temperature for 2 h. The reaction mixture was quenched with 1 M aq HCl solution (3 mL) and extracted with EtOAc (3 × 20 mL). Usual workup and purification by silica gel chromatography (hexane–EtOAc, 12:1) afforded **7a** (0.087 g, 0.41 mol 34%) and **7b** (0.14 g, 0.66 mmol 55%).
Compound **7a**: colorless oil. R_f = 0.56 (hexane–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.9 Hz, 6 H), 1.80 (br s, 1 H), 1.96 (oct, *J* = 6.6 Hz, 1 H), 4.12 (dd, *J* = 6.6, 1.5 Hz, 1 H), 6.73 (qd, *J* = 3.3, 1.5 Hz, 1 H), 7.26–7.38 (m, 5 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.0, 19.5, 32.7, 73.8, 103.0, 106.0 (q, *J* = 32.3 Hz), 123.1 (q, *J* = 274.1 Hz), 127.4, 128.6, 129.0, 131.1, 204.4 (q, *J* = 4.4 Hz). ^{19}F NMR (283 MHz, $CDCl_3$): δ = –62.44 (s). IR (neat): 692, 721, 747, 828, 920, 1001, 1029, 1074, 1127, 1210, 1273, 1369, 1387, 1411, 1462, 2874, 2934, 2963, 3429 cm^{-1}. HRMS–FAB: *m/z* calcd for $C_{14}H_{16}OF_3$ [M + H]$^+$: 257.1153; found: 257.1176.
Compound **7b**: colorless oil. R_f = 0.47 (hexane–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.6 Hz, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 1.88 (br s, 1 H), 1.96 (oct, *J* = 6.6 Hz, 1 H), 4.12 (dd, *J* = 6.6, 1.2 Hz, 1 H), 6.78 (qd, *J* = 3.3, 1.5 Hz, 1 H), 7.27–7.39 (m, 5 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.1, 19.6, 32.8, 73.6, 103.2, 106.1 (q, *J* = 32.2 Hz), 123.2 (q, *J* = 272.9 Hz), 127.6, 128.6, 129.0, 131.1, 204.1 (q, *J* = 4.3 Hz). ^{19}F NMR (283 MHz, $CDCl_3$): δ = –62.52 (s). IR (neat): 692, 719, 747, 829, 920, 1000, 1029, 1074, 1123, 1210, 1274, 1369, 1388, 1411, 1462, 1715, 1961, 2876, 2933, 2967, 3036, 3410 cm^{-1}. HRMS–FAB: *m/z* calcd for $C_{14}H_{16}OF_3$ [M + H]$^+$: 257.1153; found: 257.1187.

(10) **Procedure for the Preparation of the 2,5-Dihydrofuran 8a**
To a solution of **7a** (0.087 g, 0.41 mmol) in acetone (3 mL) was added $AgNO_3$ (12 mg, 0.082 mmol) at r.t. The solution was protected from light and stirred at that temperature for 4 d. Concentration by rotary evaporator furnished a crude mixture that was purified by silica gel chromatography (hexane–EtOAc, 20:1) to afford **8a** (0.066 g, 75%) as a pale yellow oil; R_f = 0.77 (hexane–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.9 Hz, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 2.03 (septd, *J* = 6.6, 1.2 Hz, 1 H), 5.18 (dq, *J* = 6.6, 0.9 Hz, 1 H), 5.83–5.88 (m, 1 H), 6.45 (sext, *J* = 1.8 Hz, 1 H), 7.26–7.44 (m, 5 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.5, 19.9, 32.0, 87.7 (q, *J* = 0.6 Hz), 89.3 (q, *J* = 0.6 Hz), 121.7 (q, *J* = 269.2 Hz), 126.4, 128.4, 128.7, 131.9 (q, *J* = 33.5 Hz), 135.8 (q, *J* = 4.4 Hz), 140.0. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –64.13 (s). IR (neat): 698, 726, 760, 879, 917, 1009, 1051, 1068, 1126, 1158, 1242, 1265, 1281, 1334, 1360, 2876, 2935, 2970 cm^{-1}. HRMS–FAB: *m/z* calcd for $C_{14}H_{16}OF_3$ [M]$^+$: 256.1075; found: 256.1046.