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Preparation of CF_3-Containing 1,3-Di- and 1,1,3-Trisubstituted Allenes

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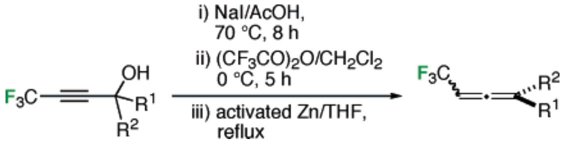
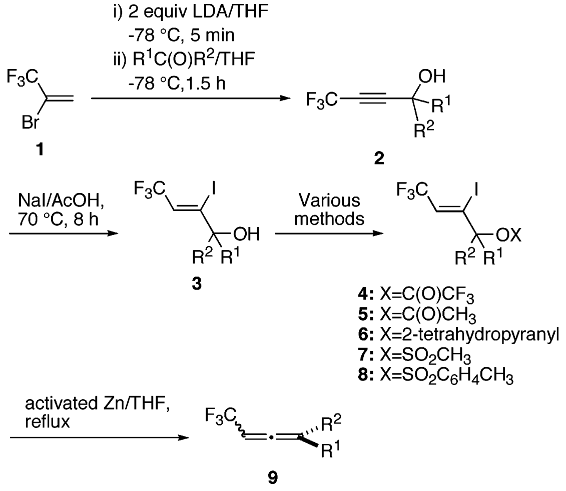


Novel synthetic pathway to access trifluoromethylated allenes with 1,3-di- as well as 1,1,3-trisubstitution patterns was developed from a variety of 4,4,4-trifluorobut-2-yn-1-ols which were then transformed into the corresponding vinylic iodides in highly regio- and stereospecific manners, and zinc-mediated β-elimination after trifluoroacetylation of the hydroxyl group eventually realized the formation of the target molecules in good to excellent overall yields in facile and short steps.

It is well-documented that introduction of fluorine atoms into organic molecules endows quite unique properties due to the special electronic character of this particular element with imposing only the slightest steric perturbation,[1] and a wide variety of fluorinated materials has been applied to such fine chemicals as pharmaceuticals, optical devices, and so forth. However, it is also this special character at least in part that renders preparation of fluorine-containing substances difficult, especially when appropriate building units with this atom around the reaction sites were utilized as starting materials. In fact, it is not rare to encounter chemical processes which do not proceed at all just by entry of a single fluorine atom to substrates while the corresponding nonfluorinated counterparts react smoothly. For this reason, we should sometimes explore independent "fine-tuned" methods for construction of the desired compounds with this special atom.

Taking the well-known importance of allenes in synthetic organic chemistry[2] into consideration, installation of fluorine atoms or fluoroalkyl groups to this framework would offer effective modification toward their original properties. However, despite such interest, only a limited number of methods can be found in the literature allowing access to these types of molecules.[3] In this paper, we would like to describe our recent development on the novel and simple preparative route to CF_3-possessing allenes starting from commercially available 2-bromo-3,3,3-trifluoropropene **1** in only four easy steps. Especially, emphasis should be placed on the fact that the present process leads to construction of various allenes of type $F_3C{-}CH{=}C{=}CHR$ whose methylated counterpart ($R{=}CH_3$) is the only one reported example to date.[3e]

SCHEME 1. Synthetic Routes to the CF_3-Containing Allenes 9



Synthetic investigation of our target allenes was initiated by the preparation of propargylic alcohols **2** totally in line with our original technique (Scheme 1).[4] Thus, treatment of commercially available 2-bromo-3,3,3-trifluoropropene **1** with 2 equiv of LDA successively affected dehydrobromination and then deprotonation of the terminal acetylenic hydrogen atom from the resultant 3,3,3-trifluoropropyne intermediate. Addition of appropriate carbonyl compounds to this reactive species smoothly furnished propargylic alcohols **2** in good to excellent chemical yields (Table 1). Transformation of **2** into the corresponding iodoalkenes **3** was performed by heating a mixture of **2** in the presence of NaI in an acetic acid solvent by referring to the protocol described by Qing et al.[5] This process realized the regio- as well as stereospecific formation of vinyl iodides **3** with (*Z*)-configuration in every instance.

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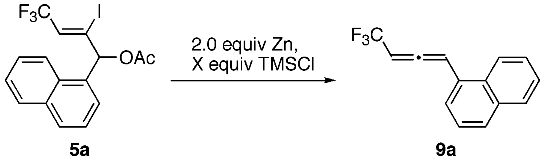
TABLE 1. Preparation of Propargylic Alcohols 2, Vinyl Iodides 3, and Hydroxy-Protected Materials 4−8

entry	compd	R^1	R^2	isolated yield (%) **2**	**3**	**4** to **8**
1	**a**	1-Naphthyl-	H	68	80	98 (**4**)
2						96 (**5**)
3						93 (**6**)
4	**b**	$PhCH_2CH_2$-	H	89	99	96 (**4**)
5						82 (**5**)
6						93 (**7**)
7						26 (**8**)
8	**c**	n-$C_{12}H_{25}$-	H	98	84	93 (**4**)
9						99 (**5**)
10						97 (**6**)
11	**d**	p-Br−C_6H_4-	H	85	85	86 (**4**)
12	**e**	o-$CH_3OC_6H_4$-	H	90	81	95 (**4**)
13						81 (**5**)
14	**f**	Ph-	CH_3-	90	72	80 (**4**)
15						74 (**5**)

TABLE 2. Investigation of the Elimination Reaction of 5a[a]



entry	solvent	X (equiv)	time (h)	isolated yield (%) **9a**	**5a**
1	THF	1.5	1.0	75	
2	THF	0	23.5	29	28
3	THF	0.1	2.5	43	5
4	Et_2O	0.1	8.5	17	82
5	THF	0.5	4.5	81	
6	Et_2O	0.5	4.5	13	87
7	CH_2Cl_2	0.5	4.5	27	63
8[b]	THF	0	0.5	74	
9[b,c]	THF	0	0.5	99	

[a] 1 mmol of **5a** was treated with zinc powder (without any special pretreatment or purification) in 5 mL of an appropriate solvent under reflux. [b] Activated zinc powder was employed. [c] The corresponding trifluoroacetate **4a** was employed as the starting material.

TABLE 3. Preparation of CF_3-Containing Allenes 9 under Various Conditions

entry	subst[b]	R^1	R^2	time (h)	prod[c]	yield of **9**[a] (%)
1	**4a**	1-Naphthyl-	H	0.5	**9a**	99
2	**5a**			2.0		74
3	**6a**			23.0		23
4	**3a**			19.0		21[d]
5	**4b**	$PhCH_2CH_2$-	H	0.5	**9b**	98
6	**4b**			0.5		92[e]
7	**5b**			7.0		67
8	**7b**			0.25		84
9	**4c**	n-$C_{12}H_{25}$-	H	0.5	**9c**	86
10	**5c**			4.0		81
11	**6c**			5.0		7
12	**4d**	p-Br-C_6H_4-	H	0.5	**9d**	87
13	**4f**	o-CH_3O-C_6H_4-	H	0.5	**9f**	87
14	**5f**			2.0		93
15	**4i**	Ph-	CH_3-	1.0	**9i**	76
16	**5i**			1.0		69

[a] Isolated yield. [b] Substrate. [c] Product. [d] Protodeiodination product of **3a** was obtained in 55% yield. [e] In the presence of 0.5 equiv of TMSCl.

With the requisite **(*Z*)-3** in hand, we turned our attention to specify adequate reaction conditions for their conversion to our targets, CF_3-containing allenes **9**. First of all, by using **3a** (R^1 = 1-naphthyl, R^2 = H) as the representative substrate, various types of leaving groups were introduced at the hydroxy function. Because of their prominent ability accepted widely, sulfonates such as **7a** and **8a** were selected at the first stage but they were proved quite unstable under the preparation conditions employed presumably due to "double activation" of these sulfonate groups at both the allylic and benzylic positions. On the other hand, ester moieties were readily incorporated, and trifluoroacetate **4a** and acetate **5a** were synthesized under the usual method in nearly quantitative yields. Compound **6a** with a tetrahydropyranyl protective group was also prepared for comparison despite its lower leaving ability.

Our synthetic plan for the final step was to transform the vinylic iodide *Z*-**3** to the corresponding organozinc species[6] for effecting the desired β-elimination: organozinc was selected because this species (i) is easy to handle, (ii) shows good chemoselectivity (usually no reaction with esters), (iii) is produced under heating condition (easily applicable to the larger yield synthesis), and so on. A THF solution containing the model acetate **5a** (R^1 = 1-naphthyl, R^2 = H) and zinc powder without any pretreatment nor purification was refluxed in the presence of an appropriate amount of trimethylsilyl chloride (TMSCl, Table 2).[7] As described in entry 1, 1.5 equiv of TMSCl enabled the smooth oxidative addition of zinc to the C−I bond in **5a** and the delivery of CH_3CO_2ZnI from the resultant intermediate furnished the expected CF_3-containing allene **9a** in 75% yield. The importance of TMSCl was clearly demonstrated by comparison of the results in entries 2, 3, and 5 with those in entry 1, and the highest yield among these examples was recorded when 0.5 equiv of TMSCl was employed. The experimental fact that even an excess amount of TMSCl did not successfully capture the reactive intermediate would be the reflection that elimination of an acetate group might simultaneously occur with organozinc formation. Et_2O and CH_2Cl_2 were also used for the construction of **9a** (entries 4, 6, and 7), but this molecule was obtained in only moderate yields in these solvents probably due to the lower refluxing temperature. Entry 8 showed intriguing information that prewashing with dilute HCl[8] was quite effective in zinc activation and a similar yield was attained in much shorter reaction time (0.5 h) without the addition of TMSCl. Almost a quantitative yield was eventually recorded when the substrate was changed to the corresponding trifluoroacetate **4a** with better leaving ability, and thus, we determined the best conditions for the production of the trifluoromethylated allenes **9** as treatment of trifluoroacetate **4** with 2 equiv of prewashed zinc powder in refluxing THF for an appropriate time.

Table 3 summarized the results of the preparation of various allenes **9** starting not only from trifluoroacetates **4** but also from substrates possessing other leaving groups for comparison. In general, trifluoroacetates **4** afforded better yields in a shorter

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(5) Qing, F.-L.; Gao, W.-Z.; Ying, J.-W. *J. Org. Chem.* **2000**, *65*, 2003.

(6) Transformation of vinyl iodide to the corresponding organomagnesium species with the methyl protection of the OH group was affected by the elimination to give the allenes. Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042.

(7) TMSCl was sometimes used as an activator of the Reformatsky reaction. See, for example: Ikegami, R.; Koresawa, A.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2003**, *68*, 2195.

(8) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, UK, 1988; p 360.

reaction period than the case of the corresponding nonfluorinated acetates **5** (entries 1 vs 2, 5 vs 7, 9 vs 10, and 15 vs 16). Interesting enough was the conversion of unprotected **3a** under the same condition, furnishing the desired allene **9a** in 21% yield; however, the main process was, as our expectation, reductive deiodination from **3a** (55% yield). As shown in entry 6 of Table 1, sulfonate **7b** from vinyl iodide **3b** was significantly smoothly transformed into **9b** in 84% yield with complete consumption of the starting **7b** after only 15 min of reflux.

In this paper, we have described our successful results for the construction of the CF_3-containing allenes **9** in a simple four-step process in good to excellent chemical yields. The advantage of the present synthetic transformation was to offer the novel as well as general pathway to access the 3-substituted 1-CF_3-allenes among which only one derivative has been reported thus far.[3e] Further synthetic application of these fluorinated allenes **9** has being investigated in this laboratory.

Experimental Section

General Procedure for the Construction of 4,4,4-Trifluorobut-2-yn-1-ols (2). The reaction with 1-naphthaldehyde is described as the representative example.

To a solution of diisopropylamine (5.61 mL, 40.0 mmol) in THF (40 mL) at 0 °C was added dropwise a 1.60 M solution of *n*-BuLi in hexane (25.0 mL, 40.0 mmol) and the mixture was stirred for 30 min at that temperature. The resultant LDA mixture was cooled to −80 °C, and 2-bromo-3,3,3-trifluoropropene (2.08 mL, 20.0 mmol) in THF (10 mL) was slowly added at −80 °C. After the solution was stirred for 5 min, 1-naphthaldehyde (2.72 mL, 20.0 mmol) was added and the whole was stirred for 1.5 h at that temperature. The reaction mixture was quenched with 1 N HCl aq (100 mL) and extracted with AcOEt three times. Concentration after drying over $MgSO_4$ furnished a crude solid that was purified by recrystallization from petroleum ether to yield the desired 4,4,4-trifluoro-1-(1-naphthyl)but-2-yn-1-ol (**2a**) (3.403 g, 13.6 mmol). Yield 68%.

General Procedure for the Construction of (*Z*)-4,4,4-Trifluoro-2-iodobut-2-en-1-ols (3).[5] The reaction with 4,4,4-trifluoro-1-(1-naphthyl)but-2-yn-1-ol (**2a**) is described as the representative example.

A solution of NaI (6.385 g, 42.6 mmol) and 4,4,4-trifluoro-1-(1-naphthyl)but-2-yn-1-ol **2a** (6.98 g, 27.9 mmol) in AcOH (42 mL) was stirred at 70 °C for 8 h. The reaction mixture was added to a beaker containing 50 mL of water, neutralized with 77.2 g (0.728 mol) of Na_2CO_3, and extracted with AcOEt three times. Concentration after drying over $MgSO_4$ furnished a crude solid that was purified by recrystallization from hexane to yield 8.508 g (22.5 mmol) of the desired 4,4,4-trifluoro-2-iodo-1-(1-naphthyl)but-2-en-1-ol (**3a**). Yield 81%.

General Procedure for the Construction of 4,4,4-Trifluoro-1-(1-naphthyl)-2,3-butadiene (9a). The reaction with 4,4,4-trifluoro-2-iodo-1-(1-naphthyl)but-2-en-1-ol (**3a**) is described as the representative example.

To a CH_2Cl_2 solution (5 mL) of 4,4,4-trifluoro-2-iodo-1-(1-naphthyl)but-2-en-1-ol (0.7562 g, 2.00 mmol) was successively added trifluoroacetic anhydride (0.42 mL, 3.0 mmol) and triethylamine (0.41 mL, 3.0 mmol) at 0 °C and the whole mixture was stirred for 5 h at that temperature. The usual workup furnished the crude **4a**, which was used for the next step without further purification.

To 1.307 g (20 mmol) of activated zinc powder in THF (10.0 mL) under argon atmosphere was added 4.619 g (9.7 mmol) of **4a** and the whole reaction mixture was refluxed for 30 min. After removal of the excess zinc by filtration, the residue was extracted three times with ether after addition of 30 mL of H_2O. The usual workup furnished a crude mixture that was purified by silica gel chromatography to furnish 2.024 g (8.64 mmol) of the desired allene **9a**. Yield 89%.

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Supporting Information Available: Full experimental details and spectroscopic data for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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