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A Novel One-Pot Conversion of Aldehydes to Trifluoromethylated Bromoallylic Alcohols

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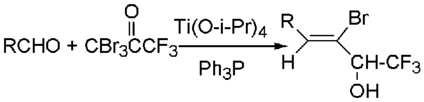
ABSTRACT



One-pot conversion of aldehydes to trifluoromethylated bromoallylic alcohols in the presence of titanium isopropoxide and triphenylphosphine is described.

Synthetic organic chemistry is one of the most rapidly developing areas in all of chemistry. Every day useful new reagents and reactions are reported worldwide in the chemical literature. Among them, functional group transformation is one of the useful and fundamental reactions in synthetic organic chemistry,[1] and hence the development of new transformations of functional groups, particularly including fluorine-containing species, is of great interest.[2] Recently vinyl bromides and their derivatives have been found to be widely used as intermediates in palladium-catalyzed Stille,[3] Suzuki[4] and other coupling reactions,[5] particularly in the synthesis of biologically active compounds.[6] Transition-metal-catalyzed substitution of allylic alcohol derivatives with nucleophilic reagents provides a highly valuable tool in synthetic organic chemistry for the formation of carbon−carbon and carbon−heteroatom bonds.[7] Thus allylic alcohols are useful intermediates in many synthetic applications,[8] especially in the synthesis of biologically active compounds.[9] Much attention has been recently devoted to the one-pot synthesis because it provides a simple and efficient route to compounds by including two or more transformations in a single operation to increase the complexity of a substrate starting from commercially available, relatively simple precursors.[10] Therefore the development of an effective method for the one-pot conversion of aldehydes to the trifluoromethylated bromoallylic alcohols would be valuable.

Recently from our laboratory one-pot carbon−carbon double bond formation has been reported.[11] Herein we describe the one-pot conversion of aldehydes to trifluoro-

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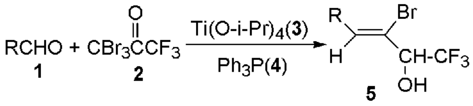
methylated bromoallylic alcohols with *Z*-stetroselectivity exclusively in 50−88% yields.

Scheme 1



The reaction is carried out in toluene. On heating equivalent amounts of aldehyde **1,** 2 equiv of tribromotrifluoroacetone **2,** 2 equiv of Ti(O^{i}Pr)$_4$ **3**, and 2 equiv of Ph_3P **4** at 100 °C for 16 h, after workup trifluoromethylated bromoallylic alcohols were obtained in moderate to good yields exclusively as the *Z*-form. No *E*-isomer was detectable from the NMR spectra and TLC data. The results are summarized in Table 1.

Table 1. Trifluoromethylated Bromoallylic Alcohols (**5**) Prepared

compound[12]	R	yield (%)[a]	*Z*:*E*[b]
5a	4-FC_6H_4	81	100:0
5b	4-ClC_6H_4	61	100:0
5c	4-BrC_6H_4	54	100:0
5d	4-$CH_3C_6H_4$	88	100:0
5e	4-$C_2H_5C_6H_4$	85	100:0
5f	4-$CH_3OC_6H_4$	84	100:0
5g	3-$CF_3OC_6H_4$	62	100:0
5h	2,4-$Cl_2C_6H_3$	68	100:0
5i	C_6H_5	54	100:0
5j	*E*-$C_6H_5CH{=}CH$	70	100:0

[a] Isolated yields. [b] The ratio of *E*- and *Z*-isomers is estimated on the basis of NMR spectra and TLC data. (NO other isomer was detectable from the NMR spectra and the TLC data).

The effect of solvent and the amounts of substrates on the reaction has been investigated with 2,4-dichlooroaldehyde **1h** as reactant. The results are summarized in Table 2. The reaction proceeds best in toluene with 2 equiv of **2**, **3**, and **4** (entry 6).

Table 2. Effect of Solvent and Amounts of Reactants on the Yields of **5h**

entry	**1**	**2**	**3**	**4**	solvent	yield (%)[a]
1	1	1	1	1	none	25
2	1	1	1	1	*n*-dibutyl ether	41
3	1	1	none	1	*n*-dibutyl ether	0
4	1	2	2	2	*n*-dibutyl ether	53
5	1	1	1	1	toluene	46
6	1	2	2	2	toluene	68
7	2	1	1	1	toluene	50

[a] Isolated yield.

To identify the configuration of products **5**, the NOESY spectrum of **5h** was performed. It shows that the CH(OH)−CF_3 group was *cis* with respect to the vinyl proton. Therefore, the double bond in compounds **5** is in the *Z*-configuration.

All compounds are new and characterized by microanalysis, IR, NMR, and mass spectroscopy.

The detailed mechanism of this reaction is being pursued.

In summary, we have developed a one-pot method for the conversion of aldehydes to trifluoromethylated bromoallylic alcohols effectively and stereoselectively. In this one-pot conversion four functionalized groups, i.e., a double bond and trifluoromethyl, bromo, and hydroxy groups, are introduced at once. This one-pot synthesis is very convenient, starting from easily available substances for the preparation of trifluoromethylated bromoallylic alcohols, and the widespread use of the vinyl bromides and allylic alcohols in organic synthesis is quite important. Thus they are interesting fluorinated building blocks, not easily available by existing synthetic methods, and would be expected to be useful intermediates in the synthesis of fluorine-containing biologically active compounds.

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Supporting Information Available: Spectral data for new compounds **5a−j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **Experimental Procedure.** To a mixture of aldehyde (1 mmol), Ph_3P (2 mmol), and toluene (3 mL) in a capped vessel under nitrogen were injected slowly Ti(O^{i}Pr)$_4$ (2 mmol) and then 3,3,3-tribromo-1,1,1-trifluoroacetone(2 mmol). After 16 h of stirring at 100 °C, the reaction mixture was treated with 5 N HCl solution (40 mL) and dichloromethane (20 mL) and extracted with dichloromethane (2 × 20 mL). The organic layer was washed with water (3 × 10 mL), dried, and evaporated to remove the solvent. The residue was chromatographed on silica gel and eluted with petroleum ether (60−90 °C)/ethyl acetate (10:1) to give the product.