Novel synthesis and application of γ-difluoromethylated prop-2-ynylic and allylic alcohols

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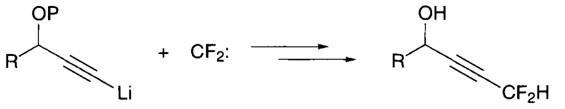
The reaction of chlorodifluoromethane with various acetylides derived from the corresponding prop-2-ynylic alcohols proceeds smoothly to afford difluoromethylated compounds in high yields; synthetic applications of the materials are also given.

The synthesis of difluoromethylated molecules is an important aspect of organofluorine chemistry due to their importance as new and effective medicines, agrochemicals and materials. Therefore, considerable efforts have been made to develop efficient and reliable as well as stereoselective routes to such compounds.[1] As widely applicable intermediates, γ-difluoromethylated prop-2-ynylic and/or allylic alcohols are attractive synthetic targets. Despite their utility, there have been no reports on the synthesis of such materials. Here we describe our preliminary findings on the preparation and the application of γ-difluoromethylated prop-2-ynylic and allylic alcohols.

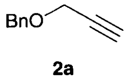
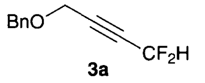
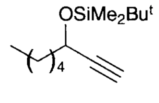
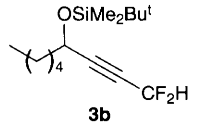
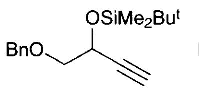
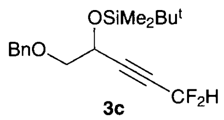
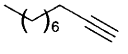
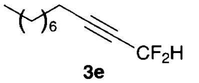
We treated a CF_2 carbene generated from CF_2HCl† with the acetylide derived from *O*-protected prop-2-ynylic alcohol (Scheme 1).

To a solution of 3-benzyloxyprop-1-yne **2a** in THF (1 mmol) was added 1.2 equiv of BuLi at −78 °C. The reaction mixture was then stirred at that temperature for 30 min. After an excess of chlorodifluoromethane was added, the mixture was stirred for 1 h at −78 °C and then gradually warmed to room temperature. After quenching with saturated aqueous NH_4Cl, the organic material was extracted with diethyl ether, washed successively with water and saturated aqueous NH_4Cl and dried over $MgSO_4$. Evaporation of the solvent afforded the crude product, which was purified by chromatography over silica gel to give the desired γ-difluoromethylated prop-2-ynylic alcohol derivative **3a** in 72% yield. The results obtained with various acetylides are summarized in Table 1.



Scheme 1

Table 1

Entry	Substrate	Product	Yield (%)[a]
1	 **2a**	 **3a**	72
2	 **2b**	 **3b**	94
3	 **2c**	 **3c**	98
4	$Ph-\equiv$ **2d**	$Ph-\equiv-CF_2H$ **3d**	87
5	 **2e**	 **3e**	86 (13)[b]

[a] Isolated yield. [b] Determined by ^{19}F NMR. The yield of byproduct in shown in parenthesis.

As shown in Table 1, lithium acetylides derived from prop-2-ynylic alcohols and phenylacetylene reacted with chlorodifluoromethane smoothly to afford the desired materials in 72–98% yields without detection of byproducts (entries 1–4). On the other hand, **2e** gave a mixture of the difluoromethylated acetylene **3e** and unknown compounds‡ which could not be separated by silica gel column chromatography (entry 5). In the reaction with acetylides derived from 4-phenylbut-1-yne and 3-phenylbut-1-yne, the formation of byproducts was observed. Thus, acetylides stabilized by an electronwithdrawing group (a phenyl or an alkoxymethyl moiety) might produce the desired difluoromethylated molecules exclusively, in contrast to non-stabilized acetylides. Furthermore, protection of a prop-2-ynylic alcohol hydroxy group with ethyl vinyl ether or transmetallation into zinc or magnesium acetylide caused a yield decrease.

A suggested carbene-mediated cycle reaction mechanism is shown in eqns. (1–4). Thus, lithium acetylide (or a slight excess

$$\underset{\text{(or BuLi)}}{R-\equiv-Li} + CF_2HCl \longrightarrow \underset{\text{(or butane)}}{R-\equiv-H} + \underset{\mathbf{4}}{CF_2Cl^-} \qquad (1)$$

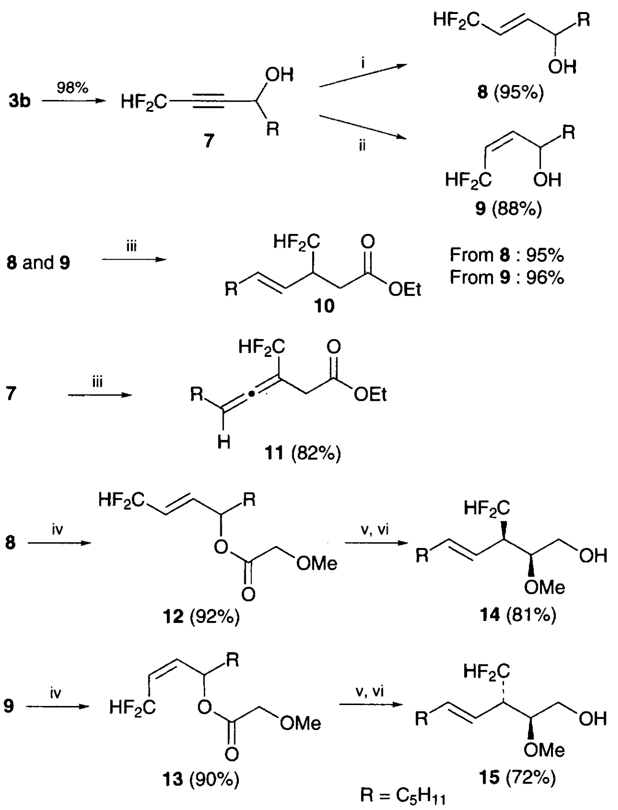
$$CF_2Cl^- \longrightarrow \underset{\mathbf{5}}{CF_2:} + Cl^- \qquad (2)$$

$$R-\equiv-Li + CF_2: \longrightarrow \underset{\mathbf{6}}{R-\equiv-CF_2^-} \qquad (3)$$

$$R-\equiv-CF_2^- + CF_2HCl \longrightarrow R-\equiv-CF_2H + \underset{\mathbf{4}}{CF_2Cl^-} \qquad (4)$$

of BuLi) might work as a base to abstract the proton of chlorodifluoromethane, affording chlorodifluoromethyl anion **4** [eqn.(1)], which might give difluorocarbene **5** by the elimination of chloride [eqn.(2)], which might react with lithium acetylide to furnish **6** [eqn.(3)]. Finally, **6** might act as a base to abstract the proton of chlorodifluoromethane, regenerating **4** [eqn. (4)].[2]

The synthetic applications of the obtained prop-2-ynylic alcohol were then investigated. Compound **3b** was transformed into the corresponding prop-2-ynylic alcohol **7** by conventional methods (TsOH–MeOH, 98% yield). According to the literature procedure,[3] **7** was treated with red-Al in toluene at −78 °C to afford (*E*)-allylic alcohol **8** in 95% yield as the sole detectable isomer. However, partial hydrogenation with a catalytic amount of Lindlar catalyst (0.01 g/1 mmol of substrate) in hexane (10 ml/1 mmol of substrate) at room temperature was problematic, giving a mixture of (*Z*)-allylic alcohol and the saturated compound. After studying the reaction conditions, it was found



Scheme 2 *Reagents and conditions*: i, Red-Al, toluene; ii, Lindlar cat., hexane, −20 °C; iii, $MeC(OEt)_3$, cat. $EtCO_2H$, 130 °C. iv, $MeOCH_2COCl$, Py; v, LHMDS, Me_3Si; vi, $LiAlH_4$

that Z-isomer **9** was obtained effectively when the reaction was performed at −20 °C using half the amount of Lindlar catalyst compared to the literature method,[3] although the product contained a slight amount of the saturated material (<5%).

The obtained (*E*)- or (*Z*)-allylic alcohols underwent Johnson–Claisen rearrangement[6] (an excess of ethyl orthoacetate and a catalytic amount of propionic acid at 130 °C in a sealed tube) to afford β-difluoromethyl-γ,δ-unsaturated ester **10** in high yields. Furthermore, ortho-Johnson rearrangement using prop-2-ynylic alcohol **7** under the same condition as described above has also been investigated and furnished the corresponding allenyl compound **11** in 82% yield (Scheme 2).

The allylic alcohols **8** and **9** were transformed into α-methoxyacetic acid (γ-difluoromethyl)allylesters **12** and **13**, respectively, substrates for [3,3]-Ireland Claisen rearrangement.[4] To a THF solution of lithium hexamethyldisilazide (LHMDS) and Me_3SiCl were added the substrates at −78 °C. The reaction mixture was then stirred for 30 min at that temperature and then warmed to room temperature. After work-up, the corresponding carboxylic acids were obtained highly diastereoselectivly (*syn*:*anti* = >99:<1 from *E*-substrate, *syn*:*anti* = 3:97 from Z-substrate),[5] and treated with $LiAlH_4$ to afford alcohols **14** and **15** in high overall yield.

Footnotes

† Obtained from F-Tech, Inc., Japan.

‡ ^{19}F NMR suggests the byproduct might be monofluorinated. On this basis, its yield was determined by ^{19}F NMR using C_6F_6 as an internal standard.

References

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2 A similar mechanism has been proposed, see: T. Tsushima, K. Kawada, O. Shiratori and N. Uchida, *Heterocycles*, 1985, **23**, 45: T. Tsushima and K. Kawada, *Tetrahedron Lett.*, 1985, **26**, 2445; I. Rico, D. Cantacuzene and C. Wakselman, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1063.
3 T. Yamazaki, K. Mizutani and T. Kitazume, *J. Org. Chem.*, 1995, **60**, 6046.
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