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Facile Synthesis of α-Trifluoromethylated Alcohols from Trifluoroacetaldehyde Ethyl Hemiacetal

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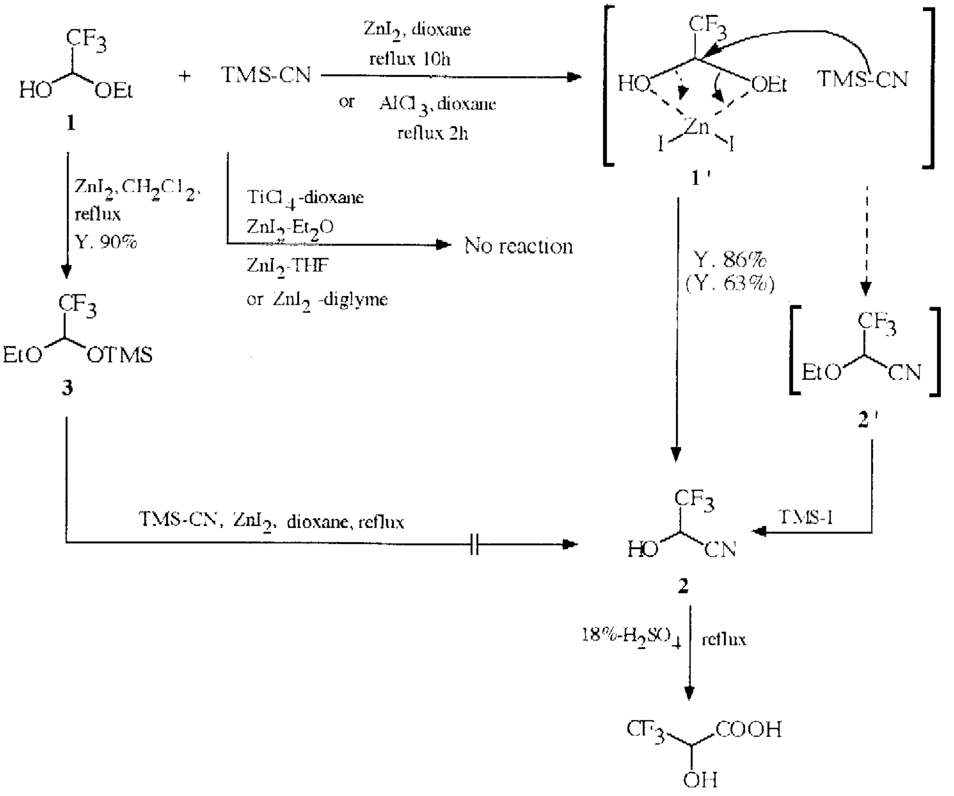
Key Words : trifluoroacetaldehyde ethyl hemiacetal; Lewis acid; trimethylsilylated nucleophiles; carbon-carbon bond formation; α-trifluoromethylated alcohol

Abstract : Trifluoroacetaldehyde ethyl hemiacetal reacted with nucleophilic organosilanes such as cyanotrimethylsilane, allyltrimethylsilane, or enol trimethylsilyl ethers in the presence of Lewis acid to afford a series of α-trifluoromethylated alcohols in high yield.

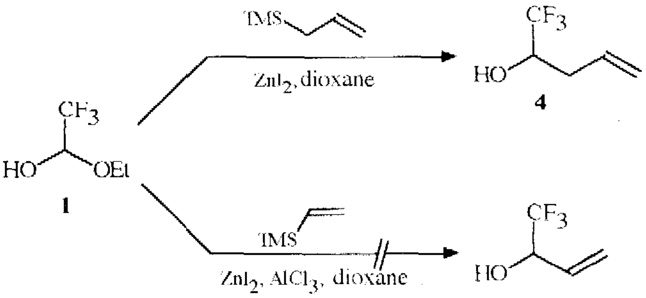
Trifluoromethylated organic compounds are of special interest and have various applications to the opto-electronic materials, pharmaceuticals and polymers.[1] As the typical preparation of α trimethylated alcohols there are reduction of α,α,α-trifluoroketones[2] and carbon-carbon bond formation of trifluoroacetaldehyde with carbon nucleophiles such as Grignard reagents and enolate anions.[3] Generally, fluorine-free aldehydes are stable than their alkyl hemiacetals. On the contrary, trifluoroacetaldehyde is gaseous and very unstable, and its alkyl hemiacetal is commercially available and stable.[4] On the other hand, there cannot be found the reports on the synthesis of alcohols by carbon-carbon bond formation using trifluoroacetaldehyde ethyl hemiacetal(**1**) except the Friedel-Crafts type alkylation yielding 1-phenyl-2,2,2-trifluoroethanol.[5] In this paper, we wish to report the synthesis of α-trifluoromethylated alcohols by the reaction of hemiacetal **1** with trimethylsilylated nucleophiles such as cyanotrimethylsilane, allyltrimethylsilane, and enol trimethylsilyl ethers in the presence of stoichiometric amount of Lewis acid in a single step.

3,3,3-Trifluoropropionitrile(**2**) was obtained in 86% yield by refluxing the mixture of **1**, zinc iodide and cyanotrimethylsilane in dioxane solvent for 10 h.[6] In this reaction, dioxane as a solvent seemed to play an important role, because in the case of dichloromethane solvent, the resulting product was not **2** but 1-ethoxy-1-trimethylsiloxy-2,2,2-trifluoroethane(**3**) which was not concerned with the formation of **2** and when diethylether, tetrahydrofuran, or diglyme solvent were used, any reaction did not occurred. In these reactions, 1-ethoxytrifluoropropionitrile(**2'**) which was thought as the possible product, was not obtained. From this fact, it is thought that the substitution of ethoxy group by nucleophilic attack of TMS-CN to acetal carbon of hemiacetal-zinc complex type intermediate(**1'**) is predominant than that of hydroxy group. If **2'** was formed, the ether bond must be cleaved by iodotrimethylsilane also formed in the system.

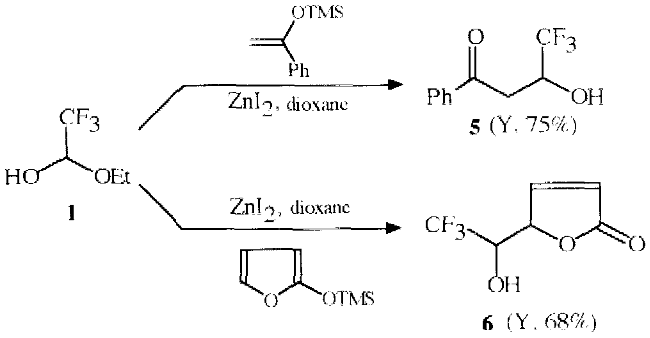
The selection of Lewis acid was important too. When aluminum chloride was used instead of zinc iodide in dioxane, only 2 h refluxing affords **2** in 63% yield, however, some side-reactions were observed. Furthermore, in the case of titanium tetrachloride, most of starting materials were recovered. The difference of reactivity resulted from kind of Lewis acids can be rationalized by the HSAB theory. The analogous carbon-carbon bond formation using trifluoroacetaldehyde *N,O*-acetals[7] and *N,S*-acetals[8] was already reported. The hydrolysis of cyanohydrine **2** under acidic condition provides an excellent route trifluorolactic acid.



The reaction of **1** with allyltrimethylsilane in dioxane in the presence of zinc iodide gave the corresponding 1-trifluoromethylated homoallylic alcohol(**4**) in 75% yield. However, the formation of allylic alcohol by the reaction of **1** with vinyltrimethylsilane under same conditions did not occur. When aluminum chloridewas used instead of zinc iodide, the desired reaction did not proceed and complicated reaction mixture was formed.



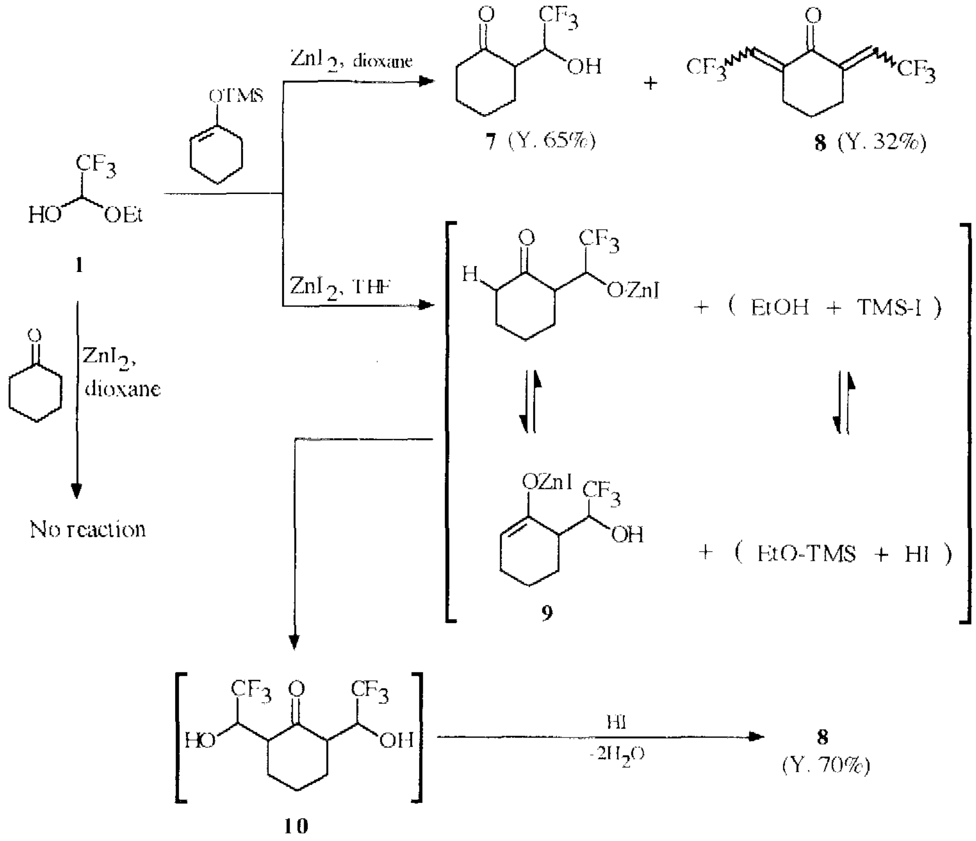
The reaction of **1** with enol trimethylsilyl ether prepared from acetophenone proceeded readily to form the corresponding β-ketoalcohol(**5**) in 75% yield. When 2-trimethylsiloxyfuran was used, α-alkylated product was not obtained but γ-(1-hydroxy-2,2,2-trifluoroethyl)-γ-butenolide(**6**) in 68% yield. When the ketones were used instead of enol silyl ethers, any reactions did not occur.



On the other hand, the use of 1-trimethylsiloxycyclohexane as a nucleophile under same conditions as above gave 2,6-bis(3,3,3-trifluoroethylidene)cyclohexane(**8**) in 32% yield based on **1** along with the corresponding aldol type product (**7**). In THF solvent, the condensation reaction proceeded to afford **8** solely in 70% yield. However, both of aldol type and condensation type reactions of **1** with cyclohexanone in the presence of zinc iodide did not occur, therefore it is thought that the zinc enolate intermediate(**9**) formed in the reaction path accelerated the second carbon-carbon bond formation and then, disubstituted cyclohexane (**10**) was dehydrated in HI-catalyzed process to form **8**.

Furthermore, it was ascertained that the similar reactions as above proceeded using trifluoroacetaldehyde methyl hemiacetal instead of **1**.

To our knowledge, the reactions described here are interesting examples of the direct carbon-carbon bond formation between hemiacetal and silylated nucleophiles, and we believe that our procedure provides the excellent route for a series of α-trifluoromethylated alcohols.



REFERENCES

1. Banks, R. E., *Organofluorine chemicals and their industrial applications* , Ellis Horwood, Chichester, **1979**; Hudlicky, M., *Chemistry of Organofluorine compounds* , 2nd edn., Ellis Horwood **1976**; Schlosser, M.,*Tetrahedron* , **1978**, *33*, 3 ; Yoshino, K.; Okazaki, M.; Taniguchi, H.; Ito, M.; Satoh, K.; Yamazaki, T.; Kitazume, T., *Japn. J. Appl. Phys.*, **1987**, *25*, L77; Welch, J. T.; Eswarakrishnan, S., *Fluorine in bioorganic chemistry,* John Wiley & Sons, Inc., **1991**.
2. For example : Yamazaki, T.; Ishikawa, N.,*Chem. Lett.*, **1985**, 889.
3. For example : Kiehlmann, E.; Loo, P. W., *Can. J. Chem.*, **1971**, *49*, 1588; Kiehmann, E.; Menon, B. C.; McGillivray, N., *ibid.*,**1973**, *51*, 3177; Pierce, O.R.; Kane, T.G., *J. Am. Chem. Soc.*; **1954**, *76*, 300; Yamazaki, T.; Takita, K.; Ishikawa, N., *J. Fluorine Chem.*, **1985**, *30*, 357.
4. Braid, M.; Iserson, H.; Lawlore, F., *J. Am. Chem. Soc.*, **1954**, *76*, 4027.
5. Guy, A; Lobgeois, A.; Lemaire, M., *J. Fluorine Chem.*, **1986**, *32*, 361.
6. Kitazume, T.; Ishikawa, N., *J. Fluorine Chem.*, **1985**, *29*, 432.
7. Fuchigami, T; Nakagawa, Y; Nonaka, T., *J. Org. Chem.*, **1987**, *52*, 5489; Fuchigami, T; Ichikawa, S; Nonaka, T, *Chem. Lett.*, **1989**, 1987; Fuchigami, T.; Ichikawa, S.; Kandeel, Z. E.; Kanno, A.; Nonaka, T., *Heterocycles*, **1990**, *31*, 415.
8. Fuchigami, T.; Yamamoto, K.; Nakagawa, Y., *J. Org. Chem.*, **1991**, *56*, 137.

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