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Allylic Fluorination

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Abstract □An efficient and inexpensive method for the substitution of allylic hydroxyl group with fluoride, without allylic rearrangement, and elimination was developed. This method consists of treating an allylic alcohol with methyllithium, followed by p-toluene sulfonyl fluoride, lithium fluoride and 12-Crown-4. This methodology was proved to be efficient by preparing geranyl fluoride, neryl fluoride, cinnamyl fluoride, E,E-farnesyl fluoride, retinyl fluoride and 4-fluoro-2-methyl-6-(*p*-tolyl)-2-heptene.

Keywords□Crown ether, Regio and stereochemical problem, Geranyl fluoride, Neryl fluoride, Cinnamyl fluoride, E,E-farnesyl fluoride, Retinyl fluoride, 4-Fluoro-2-methyl-6-(*p*-tolyl)-2-heptene.

There has been considerable interest in the synthesis and properties of fluorinated organic compounds since the remarkable enhancement of biological activity resulting from introduction of fluorine at various site in biologically active compound.[1]

Pronounced biological effects are usually seen when hydrogen atoms in a natural metabolite are replaced by fluorine.[2] This behavior is usually attributed to two properties of fluorine. First, the Van der Waals radius of fluorine. (= 1.35Å)[3] is only slightly larger than that of hydrogen (= 1.2Å). Thus, unlike other substitution, the replacement of a hydrogen atom by fluorine does not introduce large steric perturbations which might interfere with binding interactions to an enzyme or a receptor. Second, fluorine is the most electronegative of the elements.[4] Because of its electrone-withdrawing effect, fluorine may substantially alter the rate of a reaction when placed near the reaction center.[5] Such behavior is exemplified by the use of fluorinated analogues with depressed reactivities to reversibly inhibit prenyl transfer enzymes[6] or to increase the resistance of druges to oxidatives metabolism.[7]

Fluorine substituted isoprenyl derivatives have aroused interest as potential insect juvenile hormone substitutes,[8] hyperlipidaemic drugs,[9] and most recently cancer chemotherapeutic agents.[10] Especially, the fluorinated terpenes have been used for the studies of enzyme mechanism,[11-15] and for pharmacological evaluation.[10] The study of fluorinated isoprenoid, however, has been hindered by a lack of convenient methods for their synthesis.

The methods for replacing hydroxyl group by fluorine which have been developed are the following: (1) the reaction of anhydrous hydrogen fluoride,[16] HF is one of the most inexpensive fluorinating agents but its reactions generally require work under pressure due to its low boiling point. Laboratory work with HF should be conducted only in an efficient hood, with the operator wearing a full face shield and protective clothings. (2) the reaction of diethylaminotrifluorochloromethane with the free alcohols,[17] (3) the reaction of metal fluoride of tetrabutylammoniumfluoride with the corresponding tosylates,[18] (4) the reaction of phenyl tetrafluorophosphorane with silyl phenyltetrafluorophosphorane with alcohols or the corresponding ethers,[19] (5) sulfurtetrafluoride can also convert some hydroxy amino acids into the corresponding fluoro derivaties,[20] although it is mainly used in the synthesis of gemdifluorides from the corresponding carbonyls, (6) the reaction of diethylaminosulfurtrifluoride (DAST) with a hydroxyl group. Several aliphatic alcohols,[21] as well as few sugars,[22] were thus converted into the corresponding fluorides (7) Yarovenko reagent (Et_2NCF_2CHClF) which can convert a hydroxyl group with fluorine. Yields are best with primary alcohols and the reagent has been used extensively with steroids. (8) the 1 : 1 complex of SeF_4 with pyridine can also be used to prepare fluorides from alcohols,[24] (9) the reaction of CF_3OF.[25] Although this method is regarded as being mild and convenient, it often gives rise

to complex reaction mixture, in addition to the desired fluoro compound.

Several of the above methods have disadvantages such as vigorous reaction condition, low or nonreproducible yield, requirement of specialized equipment and considerable precautions, expensive cost. DAST of these is the recommended procedure for the substitution of hydroxyl group, however, DAST is extremely corrosive to human tissue, expensive and requiring specialized equipment and considerable precautions.

A survey of the literature indicated that there are no particularly satifactory methods of preparation which are simple, mild, general and inexpensive. In this connection, the development of an efficient and inexpensive method for the substitution of hydroxyl group with fluoride, in particular that of the allylic hydroxyl group is needed for the synthesis of fluorinated terpenes.

The synthesis of an allylic halide from its alcohol presents regio- and stereochemical problems not encountered with saturated compounds:

(1) The transformation should be regiospecific, leading exclusively to the α-substituted product. (2) The conditions must be such that stereochemistry at the β. γ double bond is not lost. (3) The conditions of reaction, work up, and isolation must be mild enough that neither allylic rearrangement of the product nor solvolysis/elimination occurs.

In recent years several successful methods have been reported which in certain instances overcome this problem. G. Stork and his coworkers[26] have found that allylic alcohol may readily be transformed into the corresponding chloride by treating: a solution of alcohol in ether and hexamethylphosphortriamide is treated at room temperature with an one equivalent of methyllithium in ether, followed by *p*-toluenesulfonyl chloride and lithium chloride in ether and hexamethylphosphoramide. The mixture after standing overnight at room temperature and usual work up gives directly the desired chloride.

In the light of the procedure which was done by G. Stork, *p*-toluenesulfonyl fluoride may be considered a good fluorination reagent without allylic rearrangement, which can eliminate drawback of DAST

EXPERIMENTAL METHODS

All glasswares were thoroughly dried in a drying oven and cooled down under a stream of dry nitrogen just prior to use. Most of the reagents utilized in synthesis were Aldrich Products. They were further purified by distillation when necessary. THF and diethylether were dried by refluxing with sodium metal-benzophenone, and distilled under nitrogen atmosphere.

Proton NMR spectra were recorded on Varian EM-360 spectrometer and data were given in units downfield from tetramethylsilane. NMR spectra were obtained in $CDCl_3$. Infrared spectra were taken on Perkin-Elmer Model 298 spectrophotometer. All absorbances were reported in wave numbers (cm^{-1})

Thin layer chromatography was carried out with Merck, Kiesel gel 60, PF_{254}. Column chromatography was performed with Merck kiesel gel 230-400 ASTM mesh.

General procedure for preparing allylic fluoride

A dry, three-necked roundbottomed flask is equipped with a spin bar, a dropping funnel fitted with a rubber septum, and a nitrogen inlet tube. The system is flushed with nitrogen, and allylic alcohol (10 mmole), 2.5 m/ of dry hexamethylphosphoramide, 2.5 m/ of anhydrous ether are placed in the flask. The solution is cooled to 0° with an ice-bath, and 1.6M methyllithium (10 mmole) in ether is injected into the addition funnel. The methyllithium solution is added dropwise over a period of 25 min. After the addition is complete, the funnel is rinsed by injecting 2 m/ of dry ether. To this yellow reaction mixture, is added *p*-toluenesulfonyl fluoride (10.5 mmole) in 10 m/ of anhydrous ether with stirring over a period of 20 min. 12-Crown-4 (10.5 mmole) is dissolved in dry benzene and then anhydrous lithium fluoride (10 mmole) is added. After the heterogeneous system is stirred for 30 min, the above reaction mixture is added to this heterogeneous system. The reaction mixture is warmed to room temperature and stirred for 24 hr. After stirring, 10 m/ of ether and 10 m/ of H_2O are added. The organic layer is separated and washed with H_2O, and saturated NaCl solution, and then dried over anhydrous magnesium sulfate. Evaporation affords crude product. This crude product is chromatographed on the silica gel colum. Elution with hexane/ethylacetate (9/1, v/v) gives allylic

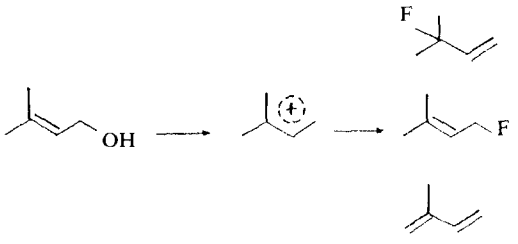
fluoride. Several different allylic alcohols were subjected to this technique and all behaved similarly under identical experimental conditions. Yields and spectral data for the allylic fluorides are given in Table 1.

RESULTS AND DISCUSSION

A variety of fluorine substituted isoprenyl derivatives have been synthesized as insecticides for studies of enzyme mechanism, and for pharmacological evaluation. The study of fluorinated isoprenoide, however, has been hindered by a lack of convenient methods for their synthesis. The main problems encountered in their synthesis from the corresponding allylic alcohol are allylic rearrangement of product (isomerization) and elimination (Scheme 1).

G. Stork and his coworkers have found that allylic alcohol may readily be transformed by a procedure: A solution of allylic alcohol in ether and HMPA was treated at room temperature with one equivalent of methyllithium in ether, followed by *p*-toluenesulfonyl chloride and lithium chloride in ether and HMPA. The mixture after standing overnight at room temperature and usual work up gave directly the desired chloride (Scheme 2).

Scheme 1.



Scheme 2.

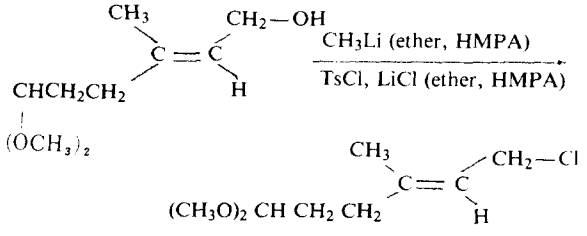
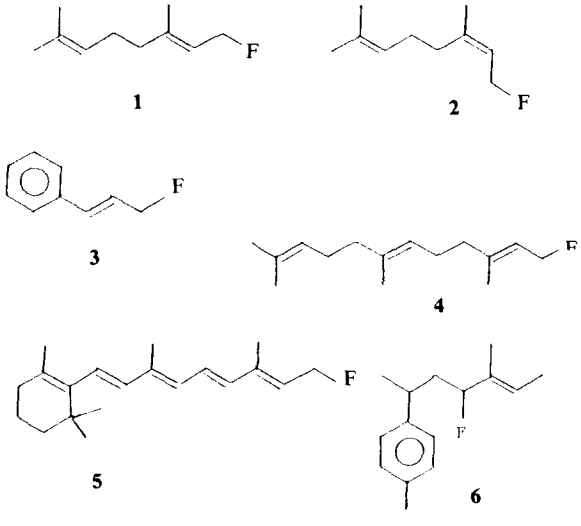


Table I. Yields and spectral data for the allylic fluorides

Allylic fluorides	IR, film (cm^{-1})	NMR ($CDCl_3$)	Yield (%)
Geranyl fluoride (**7**)	1299, 1380, 2980, 3030	1.60 (s, 3H), 1.68 (s, 6H), 2.05 (br.s, 4H), 5.05 (dd, J = 47 & 7, 2H), 5.25 (m, 1H), 5.70 (m, 1H)	63
Neryl fluoride (**8**)	1230, 1380, 2980, 3030	1.60 and 1.73 (s, 9H), 2.1 (br.s, 4H), 5.05 (dd, J = 47 & 6.5, 2H), 5.35 (m, 1H), 5.90 (m, 1H)	52
Cinnamyl fluoride (**9**)	1300, 1380, 2980, 3030	4.93 (dd, J = 47 & 7, 2H), 6.4 (dd, J = 16 & 7, 1H), 6.75 (d, J = 16, 1H), 7.5 (s, 5H)	61
E,E-Farnesyl fluoride (**10**)	1250, 1380, 1650, 2980, 3030	1.62 (s, 6H), 1.70 (s, 6H), 2.15 (br.s, 8H), 4.91 (dd, J = 47 & 7, 2H), 5.3 (m, 2H), 5.65 (m, 1H)	64
Retinyl fluoride (**11**)	1380, 1400, 1640, 2980 3030	1.0 (s, 6H), 1.5 (s, 6H), 1.7 (s, 3H), 1.9 and 2.0 (m, 6H), 4.98 (dd, J = 46 & 6, 2H), 5.65, 6.1, 6.35 (m, 6H)	58
4-Fluoro-2-methyl-6-(*p*-tolyl)-2-heptene	820, 1400, 1530, 1630 3030	1.20 (d, J = 7, 3H), 2.0 and 2.25 (each s, 6H), 2.4 (s, 3H), 2.81 (m, 2H), 3.21 (s, J = 7, 1H), 5.2 (d, J = 47, 1H), 6.3 (br.s, 1H), 6.95 (s, 4H)	61

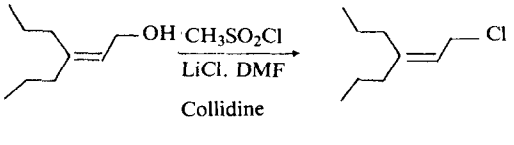
In the light of G. Stork's result, an allylic alcohol may be converted to their corresponding fluoride without allylic rearrangement by treating it with methyltithium, followed by *p*-toluenesulfonyl fluoride and lithium fluoride. Geraniol(**1**), nerol(**2**), cinnamyl alcohol(**3**), E,E-farnesol(**4**), retinol(**5**) and 2-methyl-6-(*p*-tolyl)-2-hepten-4-ol(**6**) were selected to prove this possibility.



At first, geraniol in dry hexamethylphosporamide and anhydrous ether was cooled to 0 °C with an ice bath and methyllithium in ether was added dropwise. After the addition was completes, *p*-toluenesulfonyl fluoride in dry ether was added to the red reaction mixture at 0 °C with stirring. The red color immediately disappeared upon addition. Then, anyhydrous lithium fluoride was added. The reaction mixture was warmed to room temperature and stirred overnight, After usual work up, the starting material(**1**) was recovered.

In connection with studies on insect pheromones. A.I. Meyers and his coworkers[27] developed a mild and efficient technique for converting allylic alcohol to allylic chloride (Scheme 3)

Scheme 3.

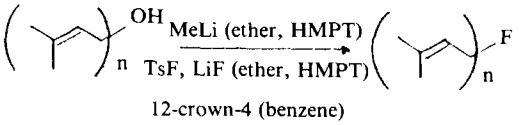


Geraniol was treated with methanesulfonyl fluoride and a mixture of lithium fluoride, N,N-dimethylformamide, and collidine at 0 °C, in accordence with this procedure. Geranyl fluoride could not be obtained in this case, either. The reaction conditions like base, temperature, solvent and reaction time were changed, but the result was not satisfactory.

Application of crown ethers in the synthesis of aryl fluoride from aryl halides has been reported.[28] The crown ethers form complexes with alkali and other metal salts which sometimes provide increased salt solubility and increased anion reactivity in aprotic organic solvents.[29-31] The ability of crown ether to make complex metal salts which are easily soluble in polar, nonpolar and aprotic solvents has prompted us to investigate the metal fluoride crown complexes in allylic fluorination of allylic alcohol.

As a modification of G. Stork's procedure the reagent prepared by dissolving 12-crown-4 in dry benzene and then adding dry lithium fluoride, was used to improve the solubility of lithium fluoride and the nucleophilicity of F^-. (Scheme 4)

Scheme 4.

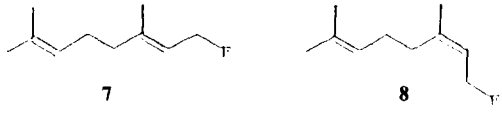


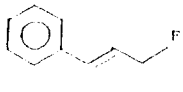
12-crown-4 (benzene)

Geraniol in hexamethylphosphoramide and anhydrous ether was cooled to 0 °C with an ice-bath. Methyllithium in ether was added dropwise. After the addition was complete, *p*-toluenesulfonyl fluoride in dry ether was added to the reaction mixture at 0 °C with stirring. The reagent was prepared by dissolving 12-crown-4 in dry benzene and the adding dry lithium fluoride. After the heterogeneous system was stirred for 30 min, the above reaction mixture was added to this heterogeneous system. The reaction mixture was warmed to room temperature and stirred for 24 hr.

The progress of the reaction was monitered by TLC. After the usual work up, the crude product was chromatographed on the silica gel column to give the desired geranyl fluoride(**7**) in 63% yield.

The structure of geranyl fluoride(**7**) was established by analysis of its spectroscopic data. The C-F strectching band lies in 1200 cm^{-1} and of medium intensity in its IR spectrum, The proton NMR spectrum of this compound(**7**) showed absorptions at δ 1.60 and 1.68 (each s) for three allylic methyl groups.





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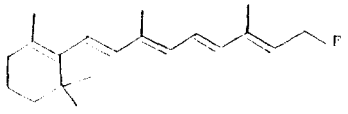

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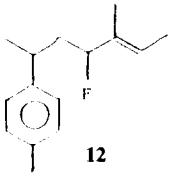

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The four hydrogens at C-4 and C-5 appeared at δ 2.05 as a broad singlet. The introduction of fluorine was accompanied by the disappearance of the OH proton singlet at δ1.35 and the appearance of a new double doublet at δ5.50. C-1 Protons coupled with the C-2 proton and the adjacent fluorine. The coupling constants are 7 and 47Hz, respectively. The chemical shifts of the olefinic proton at C-2 and C-6 in(**7**) are δ 5.25 and δ 5.70, respectively. The structures of other fluorides(**8-12**) were confirmed by analysis of their NMR data, the NMR data of these compounds were similar to that of compound(**7**).

In conclusion, an efficient and inexpensive method for the substitution of allylic hydroxyl group with fluoride has been developed in particular without the possibility of rearrangement and elimination.

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