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# A New Convenient Synthesis of Propargylic Fluorohydrins and 2,5-Disubstituted Furans from Fluoropropargyl Chloride

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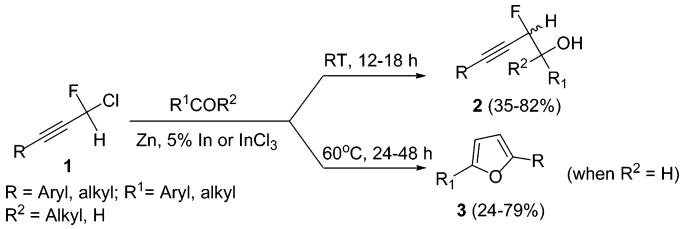


Fluoropropargyl chloride reacted with carbonyl compounds to give propargylic fluorohydrins under mild conditions and in good yields; however, at higher temperatures and longer reaction times, 2,5-disubstituted furans are obtained, also in good yields. Fluorohydrins can be readily oxidized to α-fluoroketones and α-fluorocarboxylic acids with Jones' reagent.

## Introduction

The selective substitution of hydrogen by fluorine is a valuable strategy that has made available fluoroorganic compounds with distinctive physicochemical and therapeutic properties.[1−4] In this regard, fluorohydrins have been the focus of recent attention because of their importance as intermediate and biological targets.[5−13] Typically, fluorohydrins are synthesized by an epoxide ring opening with a fluorinating agent,[14−20] but in many cases the selectivity and yield are less than satisfactory. Polysubstituted furans, such as **3**, play an important role in organic chemistry; they are not only present in many natural products and pharmaceuticals, but they also can be utilized as a molecular building block. The importance of the latter is underscored by numerous transformation reactions derived from them.[21−24] For these reasons, the syntheses of polysubstituted furans continue to attract interest among the synthetic chemistry community.

In this paper, we report the synthesis of propargylic fluorohydrins **2** under mild conditions, from a readily available fluoropropargyl chloride **1**; these fluorohydrins can be conveniently converted to 2,5-disubstituted furans **3** at higher tem-

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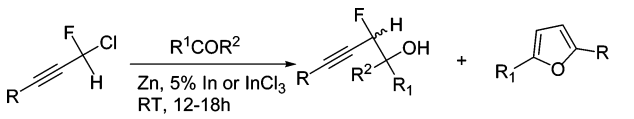
**TABLE 1. Synthesis of Fluorohydrin 2 from the Reaction of Fluoropropargyl Chloride 1 with Carbonyl Substrates**




| entry | 1 | $R^1COR^2$ | yield of 2 | yield of 3 |
|---|---|---|---|---|
| 1[a] | **1a** | $R^1 = H$; $R^2 = H$ | **2a**, 79% | not detected |
| 2 | **1a** | $R^1 = i$-Pr; $R^2 = H$ | **2b**, 70% | trace |
| 3 | **1a** | $R^1 = Ph-$; $R^2 = H$ | **2c**, 56% | 5% |
| 4 | **1a** | $R^1 = p$-Cl-$C_6H_4-$; $R^2 = H$ | **2d**, 66% | trace |
| 5 | **1a** | $R^1 = R^2 = CH_3-$ | **2e**, 82% | |
| 6 | **1a** | $R^1 = t$-Bu−; $R^2 = H$ | **2f**, 35% | 10% |
| 7[a] | **1b** | $R^1 = H$; $R^2 = H$ | **2g**, 70% | not detected |
| 8 | **1b** | $R^1 = p$-Cl-$C_6H_4-$; $R^2 = H$ | **2h**, 67% | trace |
| 9 | **1c** | $R^1 = p$-Cl-$C_6H_4-$; $R^2 = H$ | **2i**, 77% | trace |
| 10 | **1c** | $R^1 = R^2 = CH_3-$ | **2j**, 69% | trace |
| 11 | **1a** | $R^1 = n$-hexyl; $R^2 = H$ | complex mixture | |

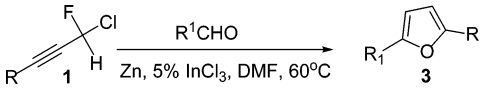
[a] Paraformaldehyde was used.

peratures and longer reaction times, and can also be smoothly oxidized, using Jones' reagent, to furnish the corresponding α-fluoroketones and α-fluorocarboxylic acids **4**.

## Results and Discussion

The zinc-mediated Barbier-type reaction is an important method in organic synthesis;[25−27] For example, we have reported the zinc-mediated reaction of TIPS monofluoropropargyl bromides (**1**, R = TIPS and Br instead of Cl) with carbonyl compounds to give fluorohydrins.[9,10] The preparation of monofluoropropargyl bromides requires the use of $CFHBr_2$, of restricted use due to the Montreal Protocol. A possible alternative would be the use of $CFHCl_2$ in a reaction with lithium acetylide. The Barbier reaction works better with a bromide or iodide, rather than chloride, because of the lower reactivity of the chloride. To get the reaction of **1** to occur, we modified the reaction conditions. DMF proved to be an effective solvent, giving more reproducible results than THF. However, in some cases we noticed that this reaction did not occur at room temperature, and when the temperature was raised, a mixture of **2** and furan **3** resulted. To coax this reaction to take place at lower temperature and eliminate the production of **3**, the use of additives that activate the zinc metal surface was sought. $InCl_3$ gave the best results. To our surprise, indium metal powder was also effective; other additives such as $Hg(OAc)_2$ and $I_2$ were less effective. Indium can also mediate this reaction in cases where a reactive substrate such as **1b** is used; $SnCl_2$, which has often been employed in this type of reaction[28,29] under similar conditions, failed completely. The newly found conditions produced **2** in good to very good yields with paraformaldehyde and *i*-butyraldehyde (Table 1, entries 1, 2, and 7), aryl aldehydes (Table 1, entries 3, 4, 8, and 9), and acetone (Table 1, entries 5 and 10). Because an aldol reaction can also occur under the reaction conditions utilized, a considerable amount of self-condensation aldol product was obtained when $R^1$ was an unbranched alkyl group (e.g., *n*-hexyl; this kind of aldehyde undergoes self-aldol condensation readily) (Table 1, entry 11), which makes the separation difficult. Typically, these reactions give a mixture of erythro and threo isomers in various ratios (from 1:1 to 16:1), erythro being the major isomer.[30]

**TABLE 2. Synthesis of 2, 5-Disubstituted Furan 3**




| entry | 1 | aldehyde ($R_1$) | time (h) | yield of 3 |
|---|---|---|---|---|
| 1[a] | **1a** | $R^1 = H$ | 48 | **3a**, 0% |
| 2 | **1a** | $R^1 = i$-Pr | 24 | **3b**, 68% |
| 3 | **1a** | $R^1 = Ph-$ | 48 | **3c**, 70% |
| 4 | **1a** | $R^1 = p$-Cl-$C_6H_4-$ | 48 | **3d**, 79% |
| 5 | **1a** | $R^1 = t$-Bu− | 48 | **3f**, 62% |
| 6 | **1c** | $R^1 = p$-Cl-$C_6H_4-$ | 24 | **3i**, 24% |
| 7 | **1c** | $R^1 = t$-Bu− | 24 | **3k**, 34% |

[a] Paraformaldehyde was used.

With an efficient synthesis of fluorohydrins **2** in hand, we turned our attention to maximize the production of disubstituted furan **3**. To our satisfaction, when higher temperatures and longer reaction times were employed, the same starting fluoropropargyl chloride **1** yielded furan **3** in good to very good yields (Table 2, entries 2−5). But when paraformaldehyde was used, no furan product was isolated (Table 2, entry 1, only compound **2a** was isolated). The low yields of **3i** and **3k** (Table 2, entries 6 and 7) might have been caused by the instability of the THP protecting group under the reaction condition.

To investigate the mechanism of the furan formation, we heated propargylic fluorohydrin **2c** in DMF for 48 h at 60 °C, but no reaction occurred, which meant that furan **3** does not derive from the propargylic fluorohydrin **2** directly. Two possible reaction pathways may operate in this reaction (Scheme 1). In mechanism A, **1** first reacts with zinc and aldehyde to give intermediate A, which then undergoes a stepwise addition−elimination, or a concerted $S_N2'$ displacement, to give the corresponding furan through a highly strained allene intermediate.[31−33] It is also possible that protonation of vinyl-zinc species B by trace amounts of a proton source (for example water) gives 3-fluoro-2,3-dihydrofuran, which undergoes dehydrofluorination to give the furan product. In mechanism B, a vicinal $S_N2$ attack by intermediate A yields a propargyl epoxide, which then isomerizes to the corresponding furan. Sham et al. had suggested that a propargyl epoxide was the intermediate in a furan formation reaction,[24] but according to other literature reports, the transformation of a propargyl epoxide to furan is catalyzed by transition metals,[34,35] acid,[36] or strong base.[37] Under

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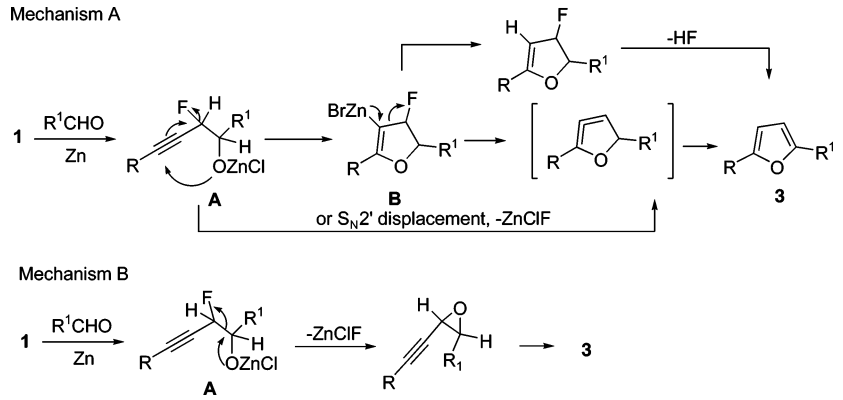
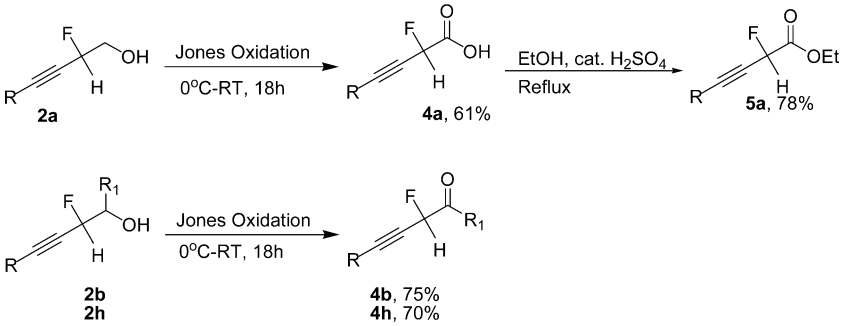
**SCHEME 1. Two Possible Mechanisms for the Formation of Furan 3**




**SCHEME 2. Preparation of α-Fluoroketones and α-Fluorocarboxylic Acids and Ester by Oxidation of Fluorohydrins 2**




our relatively milder conditions (no transition metals, no strong acid or strong base), it seems unlikely that a propargyl epoxide would be converted to furan. Thus, mechanism A is more plausible.

In principle, fluorohydrins can be oxidized to the corresponding α-fluoroketones and α-fluorocarboxylic acids, but because of the deactivating effect of α-fluorine, this oxidation is not trivial. We screened some of the most common methods used for oxidation of the alcohols (e.g., PCC or $NaClO_2$) without success. Fortunately, the classic Jones' oxidation was successful, yielding the corresponding ketones and carboxylic acid in satisfactory yields (Scheme 2)

In summary, the syntheses of fluorohydrins and disubstituted furans have been accomplished starting from a single precursor, fluoropropargyl chloride, which in turn was prepared in one step from commercially available starting materials. Fluorohydrins were efficiently converted to the corresponding α-fluoroketones and -carboxylic acids or ester with Jones' oxidation.

## Experimental Section

**Typical Procedure for the Preparation of Fluoropropargyl Chloride 1a−c:**[38] **1-Chloro-1-fluorononon-2-yne (1a).** A mixture of oct-1-yne (22.0 g, 200 mmol) in dry THF (250 mL) was cooled to −78 °C under an argon atmosphere, and then a 2.5 M solution of butyllithium in hexane (80 mL, 200 mmol) was added dropwise at −78 °C. The reaction mixture was stirred for 30 min and then cooled to −100 °C. Dichlorofluoromethane (24.8 g, 18.2 mL, 220 mmol) was added to the reaction mixture through a cannula, controlling the rate of addition to make sure the temperature did not exceed −90 °C (because the reaction is highly exothermic, a internal thermometer is recommended). After addition, the reaction mixture was allowed to warm to −50 °C, and then 100 mL of saturated $NH_4Cl$ solution was added to quench the reaction. Hexane (100 mL) was added and the organic layer was washed by water and dried over $Na_2SO_4$. After evaporation of the solvent, the crude product was purified by distillation under reduced pressure (about 90 °C/6 mmHg) to afford **1a** (11.0 g, 32%) as a colorless oil. IR (neat) 2596, 2242, 1332, 1251, 1160, 736 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.91 (t, $J$ = 7.0 Hz, 3H), 1.27−1.35 (m, 4H), 1.37−1.43 (m, 2H), 1.53−1.59 (m, 2H), 2.29−2.34 (m, 2H), 6.55 (dt, $J_1$ = 48.0 Hz, $J_2$ = 1.4 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 14.1, 18.8, 22.6, 27.9, 28.6, 31.4, 74.3 (d, $J$ = 29.5 Hz), 86.9 (d, $J$ = 233.6 Hz), 93.3 (d, $J$ = 7.6 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$) $\delta$ −119.26 (d, $J$ = 53.0 Hz); GC/MS (EI) $m/z$ 147, 121, 111, 99, 79, 67. Anal. Calcd for $C_9H_{14}ClF$: C, 61.19; H, 7.99. Found: C, 60.98; H, 8.06.

**Typical Procedure for the Synthesis of Compound 2: 2-Fluorodec-3-yn-1-ol (2a).** A 50 mL round-bottom flask equipped with a magnetic stirring bar was charged with fluoropropargyl chloride **1a** (1.76 g, 10 mmol), Zn dust (1.30 g, 20 mmol), paraformaldehyde (1.8 g, 20 mmol), DMF (10 mL), and $InCl_3$ (110 mg, 0.5 mmol). Then the reaction mixture was stirred for 24 h at room temperature, after which saturated $NH_4Cl$ solution (40 mL) was added to quench the reaction. After extraction with ether, the organic layer was washed with water and dried over $Na_2SO_4$. Purification with flash chromatography (10−30% ethyl acetate in hexane) gave pure compound **2a** (1.37 g, 79.5%). IR (neat) 3355, 2930, 2238, 1457, 1330, 1080, 851 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 7.0 Hz, 3H), 1.22−1.53 (m, 8H), 2.02−2.23 (m, 2H), 3.73−3.81 (m, 2H), 5.07−5.18 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 14.2, 22.7, 28.3, 28.6, 31.4, 60.7, 65.7 (d, $J$ = 23.4 Hz), 73.8 (d, $J$ = 25.3 Hz), 83.9 (d, $J$ = 166.9 Hz), 91.5 (d, $J$ = 10.0 Hz); $^{19}F$ NMR

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(470 MHz, $CDCl_3$) $\delta$ −180.95−180.75 (m); GC/MS (EI) *m*/*z* 140, 115, 81. Anal. Calcd for $C_{10}H_{17}FO$: C, 69.73; H, 10.14. Found: C, 69.22; H, 10.14.

**Typical Procedure for the Synthesis of Compound 3: 2-Hexyl-5-isopropylfuran (3b).** A 50 mL round-bottom flask equipped with a magnetic stirring bar was charged with fluoropropargyl chloride **1a** (176 mg, 1.0 mmol), Zn dust (130 mg, 20 mmol), *i*-PrCHO (144 mg, 2.0 mmol), and DMF (1.0 mL), followed by $InCl_3$ (11.0 mg, 0.05 mmol). Then the reaction mixture was stirred for 1 h at room temperature, warmed to 60 °C, and stirred for another 24 h. The reaction mixture was then treated with saturated $NH_4Cl$ solution (10 mL) and extracted with ether, and the organic layer was washed with water and dried over $Na_2SO_4$. Purification with flash chromatography (pure hexane to 10% ethyl acetate in hexane) gave pure compound **3b** (132 mg, 68%). IR (neat) 2962, 2659, 1565, 1465, 1014, 779 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.94 (t, $J$ = 6.5 Hz, 3H), 1.27 (d, $J$ = 7.5 Hz, 6H), 1.35−1.42 (m, 6H), 1.65−1.68 (m, 2H), 2.62 (t, $J$ = 7.5 Hz, 2H), 2.92−2.95 (m, 1H), 5.87−5.89 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 14.3, 21.4, 21.5, 22.8, 28.0, 28.1, 28.2, 29.2, 31.9, 102.9, 104.7, 154.8, 160.1; GC/MS (EI) *m*/*z* 194 ($M^+$), 179, 123, 107, 95. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.15; H, 11.41.

**Typical Procedure for the Synthesis of 4: 2-Fluorodec-3-ynoic Acid (4a).** To a mixture of **2a** (1.305 g, 7.58 mmol) in acetone (4 mL) at 0 °C was added Jones reagent (prepared from $CrO_3$ (2.27 g, 2.27 mmol), concentrated $H_2SO_4$ (2.3 mL), and water 8 mL) dropwise, and the reaction mixture was stirred overnight at room temperature. Afterward, the reaction mixture was extracted with ether (30 mL × 2), and the ether layer was combined and washed with water and dried over $MgSO_4$. Purification with flash chromatography (10−100% ethyl acetate in hexane) gave pure **4a** (0.85 g, 61%). IR (neat) 2200−3500 (b), 2929, 2239, 1743, 1425, 1232, 1047 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.86 (t, $J$ = 6.5 Hz, 3H), 1.26−1.37 (m, 6H), 1.49−1.54 (m, 2H), 2.24−2.26 (m, 2H), 5.49 (d, $J$ = 48.5 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 14.1, 18.9, 22.6, 28.0, 28.6, 31.4, 71.1 (d, $J$ = 25.7 Hz), 77.7 (d, $J$ = 184.5 Hz), 92.6 (d, $J$ = 9.1 Hz), 172.0; $^{19}F$ NMR (470 MHz, $CDCl_3$) $\delta$ −179.09 (d, $J$ = 42.8 Hz); GC/MS (EI) *m*/*z* 167, 151, 137, 121, 109, 99, 91, 81, 67. Anal. Calcd for $C_{10}H_{15}FO_2$: C, 64.50; H, 8.12. Found: C, 62.80; H, 8.17.

**Ethyl 2-Fluorodec-3-ynoate (5a).** A 100 mL round-bottom flask equipped with a magnetic stirring bar and a water condenser was charged with compound **4a** (2.5 g, 13.4 mmol) and absolute ethanol (40 mL), then concentrated $H_2SO_4$ (0.4 mL, 7.4 mmol) was added. The reaction mixture was heated to reflux and kept at reflux for 5 h, the reaction mixture was cooled to room temperature and saturated $NaHCO_3$ solution was added, then the mixture was extracted by ether, the combined organic layer was washed with water and dried over $MgSO_4$, and flash chromatography (pure hexane to 10% ethyl acetate in hexane) gave pure compound **5a** (2.24 g, 78%). IR (neat) 2933, 1769, 1457, 1206, 1058 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.84 (t, $J$ = 7.0 Hz, 3H), 1.19−1.30 (m, 9H), 1.36−1.51 (m, 2H), 2.19−2.25 (m, 2H), 4.25 (q, $J$ = 7.0 Hz, 2H), 5.38 (dt, $J_1$ = 48.4 Hz, $J_2$ = 2.0 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 14.1, 18.8, 22.6, 28.0, 28.5, 31.4, 62.5, 72.08 (d, $J$ = 25.6 Hz), 78.3 (d, $J$ = 182.1 Hz), 91.7 (d, $J$ = 9.5 Hz), 165.9 (d, $J$ = 26.3 Hz); $^{19}F$ NMR (470 MHz, $CDCl_3$) $\delta$ −178.86 (d, $J$ = 49.4 Hz); GC/MS (EI) *m*/*z* 214 ($M^+$), 195, 179, 165, 149, 121, 99, 81. Anal. Calcd for $C_{12}H_{19}FO_2$: C, 67.26; H, 8.94. Found: C, 66.97; H, 8.91.

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**Supporting Information Available:** Analytical and spectroscopic data for compounds **1c**, **2b**−**j**, **3c**−**k**, and **4b**,**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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