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Synthesis of 2,4,5-Trisubstituted 3-Fluorofurans via Sequential Iodocyclization and Cross-Coupling of *gem*-Difluorohomopropargyl Alcohols

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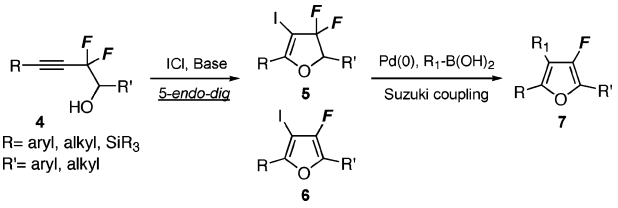
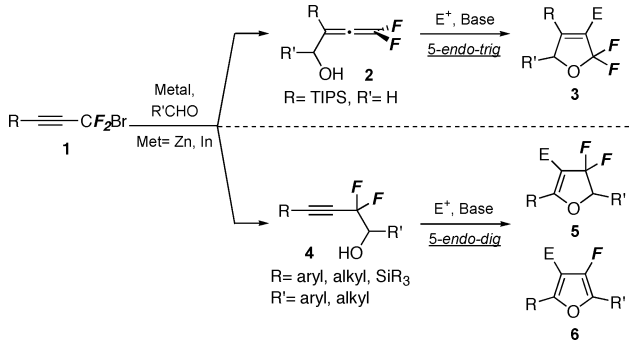


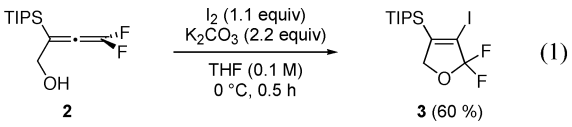
The iodocyclization of *gem*-difluorohomoallenyl and *gem*-difluorohomopropargyl alcohols with I_2 and ICl, respectively, produced the corresponding fluorinated iodofuran analogues in good yields. The iodo substituent in fluorinated 4-iodofurans was utilized as a synthetic handle to prepare multi-substituted 3-fluorofurans using a Suzuki cross-coupling reaction. The yields of both iodocyclization of *gem*-difluorohomopropargyl alcohol and subsequent Suzuki coupling were dramatically enhanced by microwave irradiation.

The furan structure is a ubiquitous unit in a variety of natural products, active pharmaceuticals, agricultural compounds, fragrances, and synthetic precursors.[1] A concise synthetic methodology for multi-substituted furans remains an important task in modern organic chemistry.[2] A particularly underdeveloped area of furan chemistry is the synthesis of its fluorine congeners,[3] despite the fact that the presence of fluorine has often enhanced the pharmacokinetic properties of a parent molecule and that many current pharmaceuticals contain fluorine(s).[4]

Our group has reported the indium-mediated selective synthesis of *gem*-difluorohomoallenyl alcohol **2** and *gem*-difluorohomopropargyl alcohol **4** from difluoropropargyl bromide **1**.[5] Both alcohols have demonstrated their usefulness as building blocks in the synthesis of fluorinated furan analogues under basic conditions (Scheme 1).[6] However, these methodologies use a proton (H^+) electrophile, which does not permit installing a synthetic handle to access multi-substituted fluorinated furans. If instead we could use a halide electrophile, we would then be able to install this reactive halide on the furan structure, which could eventually be functionalized by further cross-coupling reactions. We are now pleased to report the synthesis of fluorinated iodofurans and their conversion into 2,4,5-trisubstituted 3-fluorofurans using a Suzuki coupling reaction.

SCHEME 1. Synthetic Access to Fluorinated Furans from Alcohols 2 and 4





(1)

As a point of entry to the ensuing discussions, the iodocyclization of *gem*-difluorohomoallenyl alcohol **2** produced 2,2-difluoro-3-iodo-2,5-dihydrofuran **3** under mild conditions (1 equiv). The expected—and observed—iodocyclization pattern[7] was driven by the high electrophilicity of the *gem*-difluorovinyl carbon.[8] In marked contrast, the lesser reactivity of the triple bond in *gem*-difluorohomopropargyl alcohol **4a** hindered its

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(4) For general reviews, see: (a) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006. (b) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004 (c) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 2004. (d) Koksch, B.; Sewald, N.; Jakubke, H.-D.; Burger, K. *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996. For examples of 3,3-*gem*-difluoromethylenated nucleoacids, see: (e) Zhou, W.; Gumina, G.; Chong, Y.; Wang, J.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2004**, *47*, 3399−3408. (f) Zhang, X.; Xia, H.; Dong, X.; Jin, J.; Meng, W.-D.; Qing, F.-L. *J. Org. Chem.* **2003**, *68*, 9026−9033. (g) Patel, V. F.; Hardin, J. N.; Mastro, J. M.; Law, K. L.; Zimmermann, J. L.; Ehlhardt, W. J.; Woodland, J. M.; Starling, J. J. *Bioconjugate Chem.* **1996**, *7*, 497−510. (h) Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. *J. Org. Chem.* **1987**, *52*, 2406−2409.

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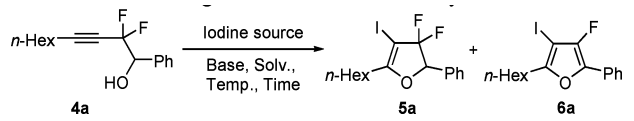
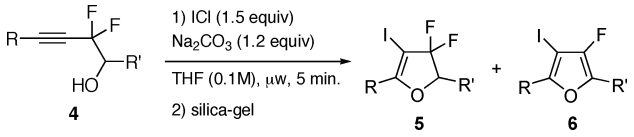
TABLE 1. Screening Conditions for the Iodocyclization of 4a



entry	base (1.2 equiv)	iodine source[a]	solvebt (0.1 M)	temp (°C)	time	yields of **5a**/**6a** (%)[b]
1	NaH	I_2	THF	reflux	12 h	complex mixture
2	NaH	ICl	THF	reflux	12 h	0/36 (6)
3	*t*-BuOK	ICl	THF	reflux	12 h	0/46 (0)
4	Na_2CO_3	ICl	THF	reflux	12 h	54/0 (37)
5	K_2CO_3	ICl	THF	reflux	12 h	9/0 (76)
6[d]	Na_2CO_3	ICl	THF	91	5 min	63/8 (0) [66][c]
7[d]	Na_2CO_3	ICl	DMF	91	5 min	50/trace (30)
8[d]	Na_2CO_3	ICl	CH_3CN	91	5 min	0/36 (0)
9[d]	Na_2CO_3	ICl	CH_2Cl_2	91	5 min	complex mixture[e]
10[d]	Na_2CO_3	ICl	toluene	91	5 min	trace/0 (64)
11[d]	Na_2CO_3	ICl	ether	91	5 min	16/23 (13)

[a] 1.5 equiv was used. [b] Yield was determined by ^{19}F NMR, and the values in parentheses refer to the amount of recovered starting material **4a**. [c] The value in brackets was the isolated yield of **6a** after silica gel chromatography. [d] The reaction was carried out in a closed vial in a microwave reactor. [e] **6a** isolated in 12% yield.

TABLE 2. Microwave-Mediated Iodocyclization of *gem*-Difluorohomopropargyl Alcohol 4



entry	R	R′	isolated yields of **5** or **6** (%)
1	*n*-Hex	Ph	66 (**6a**)
2	*n*-Hex	4−MeO−C_6H_4	62 (**6b**)
3	*n*-Hex	4−CF_3−C_6H_4	76 (**6c**)
4	*n*-Hex	$BnOCH_2$	46 (**5d**)[a]
5	$BnOCH_2$	Ph	56 (**5e**)[a]
6	Ph	Ph	49 (**5f**)[a]

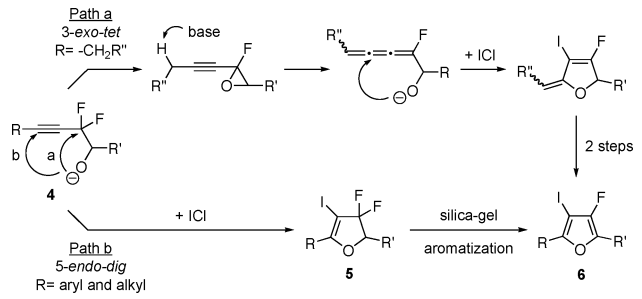
[a] Silica gel was deactivated by Et_3N.

iodocyclization, as demonstrated by the fact that strong bases, such as NaH and *t*-BuOK, caused the decomposition of product or starting material (entries 1−3, Table 1), and no reaction occurred using K_2CO_3 and a reactive electrophile (ICl) at reflux temperatures for 12 h (entry 5, Table 1). However, the combination of iodomonochloride (ICl) and Na_2CO_3 gave the desired iodocyclization product **5a** selectively, in moderate yield and with little decomposition (entry 4, Table 1).

The unreactive nature of **4a** prompted us to investigate whether microwave irradiation would hasten the desired iodocyclization (entries 6−11, Table 1). Gratifyingly, **4a** was quickly consumed to yield **5a** as a major product in satisfactory yield after only 5 min of microwave irradiation. Following silica gel chromatography, the aromatic product **6a** was obtained in 66% yield (entry 6, Table 1).

The scope of this reaction is shown in Table 2. Aryl substrates with electron-donating or -withdrawing groups at the homopropargyl position gave the corresponding 4-iodofuran **6** in good isolated yields (entries 1−3, Table 2). Interestingly, use of silica gel deactivated with triethylamine (Et_3N) furnished **5** instead of the aromatized derivative **6** (entries 4−6, Table 2).[9]

SCHEME 2. Reaction Mechanism for the Iodocyclization of 4



The published syntheses of 2,5-substituted-3-fluorofurans do not permit functionalization at the 4-position of 3-fluorofurans.[3] Thus, a readily apparent useful synthetic transformation of **5** or **6** could be the replacement of iodine with a suitable substituent using a cross-coupling reaction. An obvious approach would be the Suzuki coupling[10] of arylboronic acids. Indeed, phenylboronic acid reacted with **6a** to furnish **7aa** in excellent yield in only 0.5 h (entry 1, Table 3). Microwave irradiation proved critical for the efficiency of this reaction since the same reaction at reflux not only failed to consume **6a** after 12 h but also led to the formation of byproducts. Electron-rich or electron-deficient aryl boronic acids reacted with **6a** in satisfactory yields (entries 2−6, Table 3). Furthermore, 3-thienylboronic acid (entry 7, Table 3) and (*E*)-cinnamylboronic acid (entry 8, Table 3) gave the corresponding sp^2-sp^2 coupling products in good and moderate yields, respectively, with only a slight change in the reaction time. Notably, the Suzuki coupling of **5** spontaneously yielded only **7** (entries 11−13, Table 3), with no trace of the corresponding 4,5-dihydrofuran.

The two proposed mechanisms for the iodocyclization of **4** are depicted in Scheme 2. Initial deprotonation of **4** by a base gives rise to an oxyanion, which can then attack either on the CF_2 carbon in a 3-*exo-tet* fashion (Path a, Scheme 2)[11] or on the triple bond in a 5-*endo-dig* fashion (Path b, Scheme 2).[12,13] The conversion of acetylenic epoxide intermediates into furans via their cumulene intermediates, in the presence of bases, has been reported.[14] However, for this transformation to occur, alkyl substrates are required on R. Fortunately, we were able to recrystallize **5f** and obtain an X-ray analysis (Figure 1), which, in turn, allowed us to use the ^{19}F NMR spectral data of crude **5** (prior to aromatization) to confirm that, in all cases, 3,3-difluoro-4-iodo-4,5-dihydrofuran **5** was produced, regardless of the substrates R and R′. This experimental fact shored up support for Path b as the most likely mechanism for our reaction. The

(9) The use of normal silica gel for isolation resulted in the decomposition of the benzyl ether group (entries 4 and 5, Table 2) and a difficult separation from byproducts (entry 6, Table 2).

(10) For reviews of the Suzuki−Miyaura cross-coupling, see: (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419−2440. (b) Kotha, S.; Lahiri, K.; Kaschinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

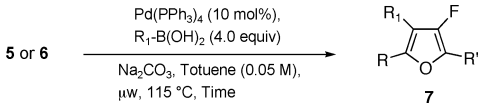
(11) A similar base-mediated cyclization of *gem*-difluorohomopropargyl alcohol was reported. This report claimed that 3-fluoro-2,5-substituted furans were obtained via a 3-*exo-tet* cyclization. See ref 3d.

(12) El-Taeb, G. M. M.; Evans, A. B.; Jones, S.; Knight, D. W. *Tetrahedron Lett.* **2001**, *42*, 5945−5948.

(13) A cyclic iodonium ion intermediate has been proposed. See: Barluenga, J.; Rodríguez, M. A.; Campos, P. J. *J. Org. Chem.* **1990**, *55*, 3104−3106 and references cited therein.

(14) (a) Marshall, J. A.; Dubay, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1450−1456. (b) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1991**, *56*, 1685−1687.

TABLE 3. Microwave-Mediated Suzuki Coupling of 5 or 6



entry	R	R′	R_1	time[a] (h)	isolated yield of **7** (%)
1	*n*-Hex	Ph (**6a**)	Ph	0.5	98 (**7aa**)
2	*n*-Hex	Ph (**6a**)	3,4-(OCH_2O)−C_6H_3	0.5	78 (**7ab**)
3	*n*-Hex	Ph (**6a**)	4-CHO−C_6H_4	1.5	72 (**7ac**)
4	*n*-Hex	Ph (**6a**)	4-CN−C_6H_4	1.0	63 (**7ad**)
5	*n*-Hex	Ph (**6a**)	4-F−C_6H_4	0.5	66 (**7ae**)
6	*n*-Hex	Ph (**6a**)	4-CF_3-C_6H_4	0.5	63 (**7af**)
7	*n*-Hex	Ph (**6a**)	3-thienyl	1.0	71 (**7ag**)
8	*n*-Hex	Ph (**6a**)	(*E*)-PhCHCH_2	1.5	58 (**7ah**)
9	*n*-Hex	4-MeO−C_6H_4 (**6b**)	Ph	2.0	85 (**7ba**)
10	*n*-Hex	4-CF_3-C_6H_4 (**6c**)	Ph	1.0	75 (**7ca**)
11	*n*-Hex	$BnOCH_2$ (**5d**)	Ph	1.5	50 (**7da**)
12	$BnOCH_2$	Ph (**5e**)	Ph	1.0	51 (**7ea**)
13	Ph	Ph (**5f**)	Ph	1.5	77 (**7fa**)

[a] Reaction progress was monitored by TLC or GC−MS.

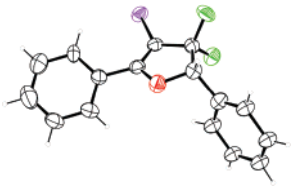


FIGURE 1. Single-crystal X-ray structure of **5f**.

electronically deficient nature of the alkyne moiety in **4** had been verified through DFT calculations.[3b]

In summary, whereas the iodocyclization of *gem*-difluorohomoallenyl alcohol **2** produced 2,2-difluoro-3-iodo-2,5-dihydrofuran **3** at low temperature, the iodocyclization of *gem*-difluorohomopropargyl alcohol **4** required use of microwave irradiation to yield 3,3-difluoro-4-iodo-4,5-dihydrofurans **5** or 3-fluoro-4-iodofurans **6** in satisfactory yields. This investigation clearly demonstrated that the iodocyclization proceeds via a 5-*endo-dig* mode on the electronically deficient triple bond. Finally, fluorinated 4-iodofuran analogues **5** and **6** were successfully used in the synthesis of fully substituted 3-fluorofurans **7** by microwave-mediated Suzuki coupling.

Experimental Section

2,2-Difluoro-3-iodo-4-triisopropylsilyl-2,5-dihydrofuran (3). To a solution of I_2 (0.55 mmol, 1.1 equiv) and K_2CO_3 (1.1 mmol, 2.2 equiv) in THF (4.0 mL) was added a solution of difluorohomoallenyl alcohol **2** (0.5 mmol, 1.0 equiv) in THF (1.0 mL) at 0 °C. The resulting mixture was stirred for 0.5 h at 0 °C, then the reaction mixture was quenched by H_2O (20 mL) and extracted by Et_2O (10 mL × 3). The combined organic layer was washed by 5% aqueous solution of saturated sodium bisulfite (10 mL × 1) and then dried over $MgSO_4$. The desired product was isolated by flash silica gel chromatography with hexane as an eluent, after which **3** (116 mg, 60%) was obtained as a white crystal: ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 18H), 1.45 (m, 3H), 4.84 (t, J = 11.3 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −61.18 (s); ^{13}C NMR ($CDCl_3$) δ 11.3, 18.6, 81.9, 92.2 (t, J = 38.0 Hz), 132.2 (t, J = 249.5 Hz), 151.7; IR (CCl_4) 2949, 2870, 1577, 1461, 1348, 1257, 1174 cm^{-1}; mp = 33−34 °C; MS *m*/*z* (%) 371 (100), 195 (5), 158 (5). Anal. Calcd for $C_{13}H_{23}F_2IOSi$: C, 40.21; H, 5.97. Found: C, 40.49; H, 5.95.

3-Fluoro-5-*n*-hexyl-4-iodo-2-phenylfuran (6a). An oven-dried microwave vial (10 mL size) fitted with a stir bar, under argon atmosphere, was charged with sodium carbonate (0.6 mmol, 1.2 equiv) into which *gem*-difluorohomopropargyl alcohol **4a** (0.5 mmol) in THF (2.0 mL) was added via syringe. The mixture was stirred vigorously for 10 min before being cooled in an ice bath for 5 min followed by slow addition of iodine monochloride (0.75 mmol, 1.5 equiv) in THF (3.0 mL). The vial was then placed in a CEM Discover microwave synthesizer at 91 °C for 5 min (at 150 W, 250 psi max), and the temperature was monitored by the microwave-attached computer during the reaction. After cooling to room temperature, the reaction was quenched with aqueous sodium bisulfite (12.0 mL, 3/1 = water/saturated sodium bisulfite). The mixture was extracted with ether, and the combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The organic solvent was carefully removed in vacuo treating with ca. 1.0 g of silica gel to induce aromatization. The resulting powder was placed on top of a silica gel column chromatograph and eluted with hexane to furnish **6a** (122 mg, 66%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.92−0.94 (m, 3H), 1.36−1.40 (m, 6H), 1.69−1.74 (m, 2H), 2.72 (dt, J = 2.0, 8.0 Hz, 2H), 7.27 (dt, J = 1.5, 6.5 Hz, 1H), 7.43 (dt, J = 2.0, 8.5 Hz, 2H), 7.67 (dd, J = 1.5, 7.0 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −159.21 (s, 1F); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.5, 27.8, 28.0, 28.6, 31.4, 57.6 (d, J = 24.1 Hz), 123.2 (d, J = 4.3 Hz), 127.0, 128.6, 128.7, 135.1 (d, J = 20.1 Hz), 149.7 (d, J = 253.8 Hz), 154.1 (d, J = 4.8 Hz); IR (neat) 3057, 2927, 2857, 1943, 1872, 1634, 1495, 1417, 1147, 1017, 759 cm^{-1}; MS *m*/*z* (%) 373 (100, M^+ + H), 372 (14), 302 (44), 246 (3), 176 (6), 106 (9); HRMS (EI) calcd for $C_{16}H_{18}FIO$ (M^+) 372.0386, found 372.0375.

3-Fluoro-5-*n*-hexyl-2,4-diphenylfuran (7aa). An oven-dried microwave vial (10 mL size) fitted with a stir bar under argon atmosphere was charged with $Pd(PPh_3)_4$ (0.035 mmol, 10 mol %) and phenylboronic acid (1.4 mmol, 4.0 equiv), into which 3-fluoro-4-iodofuran **6a** (0.35 mmol) was added along with EtOH (0.5 M relative to **6a**), 0.35 mL of aqueous Na_2CO_3 (0.2 g/mL), and toluene (0.05 M). The vial was then capped under argon and placed in a CEM Discover microwave synthesizer at 115 °C for 30 min (at 150 W, 250 psi max), and the temperature was monitored by the microwave-attached computer during the reaction. After cooling to room temperature, the reaction mixture was quenched with saturated NH_4Cl followed by extraction with ether. The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified on a silica gel column chromatograph eluted with hexane affording product **7aa** as a colorless oil (111 mg, 98% yield): ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.0 Hz, 3H), 1.31−1.44 (m, 6H), 1.77

(quintet, $J = 7.5$ Hz, 2H), 2.79 (t, $J = 8.0$ Hz, 2H), 7.28 (t, $J = 7.0$ Hz, 1H), 7.37−7.40 (m, 1H), 7.44−7.48 (m, 6H), 7.76 (d, $J = 8.0$ Hz, 2H); ^{19}F NMR ($CDCl_3$) δ −166.21 (s, 1F); ^{13}C NMR ($CDCl_3$) δ 4.0 (d, $J = 11.6$ Hz), 22.5, 27.2 (t, $J = 11.5$ Hz), 28.2, 28.9, 31.5, 114.8 (d, $J = 15.3$ Hz), 123.2 (d, $J = 16.3$ Hz), 126.6 (d, $J = 16.4$ Hz), 127.2 (d, $J = 22.1$ Hz), 128.5, 128.7, 129.3 (d, $J = 4.8$ Hz), 130.2, 134.3 (d, $J = 20.3$ Hz), 141.2, 147.8 (d, $J = 256.0$ Hz), 150.1 (d, $J = 4.8$ Hz); IR (neat) 3058, 2954, 2927, 2856, 1945, 1872, 1802, 1749, 1645, 1499, 1421 cm^{-1}; MS *m*/*z* (%) 322 (2, M^+), 254 (71), 233 (3), 205 (2), 106 (6). Anal. Calcd for $C_{22}H_{23}FO$: C, 81.95; H, 7.19. Found: C, 81.91; H, 7.31.

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Supporting Information Available: Analytical and spectroscopic data for **6b**,**6c**, **5d**−**5f**, **7ab**−**7ah**, and **7ba**−**7fa** and CIF information for **5f**. This material is available free charge via the Internet at http://pubs.acs.org.

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