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Electrophilic Cyclizations of 2-Fluoroalk-3-yn-1-ones: Room-Temperature Synthesis of Diversely 2,5-Disubstituted 3,4-Fluorohalofurans

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A 5-*endo*-*dig* halocyclization of 2-fluoroalk-3-yn-1-ones with the use of *N*-iodo- and *N*-bromosuccinimide, in the presence of gold chloride/zinc bromide (5:20 mol-%, dichloromethane), under ambient conditions, provides a facile method for the synthesis of 2,5-disubstituted 3-bromo-4-fluoro- and 3-fluoro-4-iodofurans. The sequential procedure starts at monofluorination of the alk-1-en-3-yn-1-yl silyl ethers with Selectfluor and proceeds with good overall yields (62–78 %).

Introduction

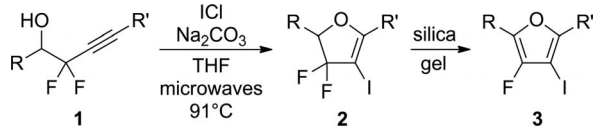
The furan motif is found in biologically active natural and artificial compounds.[1] Extension of practical applications of furans include synthetic organic chemistry or materials science.[2] Although a variety of methodologies and protocols have been reported, the synthesis of highly substituted furans remains the subject of intensive development in recent years.[3] Since furans undergo electrophilic and metalation reactions more readily at α-positions (C-2 and C-5) and are also sensitive to an acidic environment, the synthesis of a diverse collection of substituted furans remains a challenge. In general, substituted furans are accessed by ring derivatization or cyclization of acyclic precursors. Among the variety of compounds that can be subjected to cyclization, unsaturated alcohols or ketones are naturally the most attractive substrates.[4]

Halofurans, important synthetic derivatives, provide an opportunity for further functionalization. In particular, iodo- and bromofurans are useful substrates for a variety bond-forming reactions,[5,6] and also serve as building blocks for combinatorial chemistry.[7]

Pharmaceutical components containing fluorine have found a wide application in medicinal chemistry.[8] Since the furan ring constitutes a submotif encountered in lead compounds, corresponding fluorinated molecules are potentially sought-after building blocks. Indeed, fluorofuran or (perfluoroalkyl)furan fragments have already been embedded within structures possessing important pharmacological properties.[9] Recently, we have reported gold-catalyzed cycloisomerization of 2-fluoroalk-3-yn-1-ones as a tool for the synthesis of unsymmetrically 2,5-disubstituted 3-fluorofurans.[10] This method is essentially limited to the synthesis of trisubstituted furans.[11] Upon considering the pharmaceutical potential, as well as the limitations of available synthetic methods for 2,4,5-trisubstituted 3-fluorofurans, we decided to pursue the development of their synthesis.

Electrophilic halocyclization reactions offer an efficient and potent methodology for the preparation of functionalized heterocycles by tandem isomerization/halogenation processes.[12–14] The electrophilic component serves as both a cyclization catalyst and halogen donor, thus creating a very effective process from the standpoint of material economy.

To the best of our knowledge, the only reported synthesis of 3-fluoro-4-iodofurans is described by the Hammond group, and is based on an iodocyclization reaction.[5] The unreactive nature of *gem*-difluorohomopropargyl alcohols (2,2-difluoroalk-3-yn-1-ols) **1** requires a combination of strong electrophile (ICl), base (Na_2CO_3), and microwave irradiation (91 °C), to access 3,3-difluoro-4-iodo-2,3-dihydrofurans **2**. Subsequent silica gel aromatization leads to the desired 3-fluoro-4-iodofurans **3** (Scheme 1). Only one example of 3-bromo-4-fluorofuran, with undisclosed preparative yield, has been prepared by a sequential lithiation/bromination reaction of 3-fluoro-2,5-diphenylfuran.[15]



Scheme 1. Synthesis of 3-fluoro-4-iodofurans **3** from *gem*-difluorohomopropargyl alcohols **1** (R = aryl; R′ = alkyl).[5]

These known strategies leading to β-halogenated fluorofurans rely on the same intermediate, *gem*-difluorohomopropargyl alcohol.[16] The first step of its preparation involves bromine substitution of bromochlorodifluoromethane with lithium acetylide, at or below –100 °C. Production

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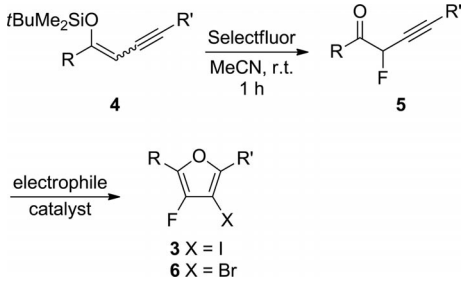
of CF_2ClBr, known as Halon1211 or Freon12B1, has been discontinued in most countries. The follow-up Barbier reaction with aldehydes proceeds at the cost of losing another halogen.[17] In addition, aromatization includes elimination of hydrogen fluoride, either on silica gel or by DBU. Apparently, these cumulative steps do not make use of halogens efficiently in the sense of economy, yields, and practicality. Thus, we sought to develop a more effective, especially in terms of halogen atom economy, synthesis of highly and diversely substituted fluorofurans.

Results and Discussion

We decided to introduce fluorine into an acyclic skeleton and to investigate the electrophilic iodo/bromocyclization of 2-fluorobut-3-yn-1-ones. A reverse order of introduction of halogens was not pursued, since initial effort to facilitate electrophilic fluorocyclization of non-fluorinated but-3-yn-1-one with Selectfluor was not successful.

The electrophilic halocyclization reaction was explored by using phenyl/*p*-tolyl-substituted model substrate. Since monofluorination of silyl enol ethers **4** (readily available from alky-3-yn-1-ones[18]) proceeds at room temp. with almost quantitative yield, a sequence of consecutive fluorination and halocyclization reactions, without isolation of 2-fluoroalkynones **5**, was used (Scheme 2).



Scheme 2. Synthesis of fluorohalofurans **3** and **6** by a sequence of fluorination/electrophilic cyclization of **4** (for R, R′ see Table 2).

When crude ketone **5a** (R = Ph, R′ = *p*-MeC_6H_4) was treated with NIS (1.2 equiv.) at ambient temperature, the iodocyclization reaction proceeded slowly. A small-scale reaction mixture (0.100 mmol, 0.05 M in anhydrous CH_2Cl_2) was analyzed by ^{19}F NMR after 20 h. Approximately 50% of the fluorobutynone was converted, with 40% accounting for the sought 3-fluoro-4-iodofuran **3a** (Table 1, Entry 1).

Increasing the temperature has a positive impact, but only to some extent. When the reaction mixture was refluxed in CH_2Cl_2 for 18 h, the desired product **3a** was successfully separated by column chromatography with 45% yield (Entry 2). Microwave assistance (80 °C, 40 min) did not provide an advantage over conventional heating (Entry 3). Thus, an enhancement of the electrocyclization procedure with the aid of a catalytic system was sought.

By comparison, the non-fluorinated butynone undergoes a clean iodocycliztion reaction at room temp. within practically 0.5 h.[14b] The low reactivity of monofluorobutynone is likely caused by the fluorine atom electron-withdrawing effect, which diminishes the alkyne's nucleophilicity towards the electrophile (halogen) as well as the oxygen nucleophilicity. A thwarting influence of the fluorine atom was also observed during the cycloisomerization process of fluorinated alkynones. Although the conversion of alk-3-yn-1-ones to furans may be quantitatively accomplished at room temperature within minutes by using simple Lewis acids such as zinc chloride or other transition metals,[18,19] the analogous reaction of 2-fluoroalk-3-yn-1-ones requires the use of a gold catalyst.[10]

Table 1. Optimization of halocyclization of fluorobutynone **5a**.

Entry	Electrophile[a]	Catalyst[b]/additive[c]	Time	Yield[d]
1	NIS	–/–	20 h	40%[e]
2	NIS	–/–	18 h[f]	45%
3	NIS	–/–	40 min[g]	35%[h]
4	NIS	AuCl/–	16 h	53%
5	ICl[i]	AuCl/–	16 h	21%
6	NIS	AuCl/TsOH·H_2O	30 min	44%[j]
7	NIS	AuCl/TsOH·H_2O	6 h	63%
8	NIS	AuCl/TsOH·H_2O	16 h	40%
9	NIS	AuCl/NH_4Cl[k]	30 min	59%
10	NIS	AuCl/$ZnBr_2$	10 min	76%
11	NIS	$ZnBr_2$	1 h	57%[e]
12	NBS	AuCl/$ZnBr_2$	10 min	62%[l]

[a] 1.2 equiv., dichloromethane, room temp., unless indicated otherwise. [b] 5 mol-%. [c] 20 mol-%, unless indicated otherwise. [d] **3a**, isolated by chromatography, unless indicated otherwise. [e] Reaction on a 0.100 mmol scale, 0.05 M; conversion determined by ^{19}F NMR spectroscopy. [f] Reflux. [g] The reaction was conducted in a microwave oven on a 0.500 mmol scale at 80 °C. [h] The product contained traces of impurities. [i] 1.5 equiv. [j] Reaction on a 0.250 mmol scale, 0.025 M; conversion determined by ^{19}F NMR spectroscopy. [k] 100 mol-%. [l] 3-Bromo-4-fluoro-2-(4-methylphenyl)-5-phenylfuran (**6a**).

Alkyne activation with the use of acids, iodine, or gold complexes was reviewed recently.[20] Especially gold(I) complexes have proved to be excellent π-electrophilic Lewis acids.[21] Since the intermediate vinylgold species[22] has been claimed to be trapped by electrophilic halogens,[23] we surmised that the combination of a suitable catalyst and a source of halogen may offer an effective route leading to 3,4-dihalofurans. Gratifyingly, we observed that the combination of AuCl/NIS (5 mol-%:1.2 equiv.) in CH_2Cl_2 yielded at ambient temperature, after 16 h, 3-fluoro-4-iodofuran **3a** with 53% yield (Entry 4). To our delight, formation of the competitive proton analogue (3-fluorofuran) was not observed.

Replacement of NIS by a stronger electrophilic reagent, iodine monochloride, as the source of halogen did not warrant further attention since the product **3a** was isolated in only 21% yield (Entry 5). The formation of an abundant byproduct was observed in the post-reaction mixture by GC/MS. The release of hydrogen chloride most likely creates an interfering acidic environment. Neutralization by addition of a base was not attempted since a similar 2-fluoroalk-3-yn-1-one quickly isomerizes to allenyl ketone in the presence of K_2CO_3.[24]

We focused our attention on *N*-halosuccimides, halogenating reagents superior to elemental halogen regarding its convenient handling and efficiency of halogen use. Engagement of the carbonyl oxygen atom in *N*-halosuccimide in interactions with Brønsted or Lewis acids may enhance dissociation into electrophilic halogen and thus increase the halogenating ability.[25] While the catalyst may have a Lewis acid type interaction with the NIS, stimulating the succinimide to be a more active "I^+" donor, it was anticipated that the carbophilic gold(I) catalyst would rather associate with the alkyne functionality during the reaction. Thus, an auxiliary catalyst was introduced to enhance the heterolytic dissociation of NIS. According to literature reports on the electrophilic activity of halosuccinimides, we examined the influence of *p*-toluenesulfonic acid monohydrate[26] and, in a separate experiment, ammonium chloride.[27] In the presence of $TsOH·H_2O$ (20 mol-%), the halocyclization reaction was significantly accelerated. After 30 min, 6 h, and 16 h the yields of 3-fluoro-4-iodofuran **3a** were 44%, 63%, and 40%, respectively (Entries 6–8). When NH_4Cl (1 equiv.) was suspended in the presence of AuCl and NIS, the reaction was also effectively completed within 30 min and with 59% of isolated yield of **3a** (Entry 9). The replacement of the Brønsted acid by a Lewis acid, $ZnBr_2$ (20 mol-%),[28] further accelerated and increased the efficiency of the gold-assisted halocyclization. The reaction was completed within 10 min, and 76% of halofuran **3a** was isolated (Entry 10).[29] During the control experiment, in the absence of AuCl, the formation of more side products was observed (Entry 11). Thus, the conditions used in Entry 10 were extended for the bromocyclization reaction. In an analogous manner, bromofuran **6a** was obtained with 62% yield, when NBS was used as an electrophile (Entry 12).

The preparative synthesis of a series of fluorofurans was carried out on a small scale (0.50 mmol). Although we focused on aryl substituents, we also examined one compound containing a cycloalkyl group. The explored substituents are provided in Table 2.

Table 2. Preparation of 3-fluoro-4-iodo- and 3-bromo-4-fluorofurans **3** and **6**, respectively.

Entry	Enol ether	R	R′	Furan	Yield[a]
1	**4a**	C_6H_5	*p*-MeC_6H_4	**3a**	76%
2				**6a**	62%
3	**4b**	*p*-FC_6H_4	*p*-MeC_6H_4	**3b**	68%
4				**6b**	72%
5	**4c**	*p*-BrC_6H_4	*p*-MeC_6H_4	**3c**	69%
6				**6c**	68%
7	**4d**	*p*-BrC_6H_4	*p*-*t*BuC_6H_4	**3d**	63%
8				**6d**	65%
9	**4e**	C_6H_5	*c*-C_3H_5	**3e**	70%
10				**6e**	78%

[a] Reactions were carried out on a 0.50 mmol scale with Selectfluor (0.55 mmol) in MeCN, NIS or NBS (0.60 mmol), and $AuCl/ZnBr_2$ (5:20 mol-%) in CH_2Cl_2, at room temp.; reaction time 1 h + 10 min.

The composition of the new 3,4-dihalofurans was confirmed by NMR, MS, and IR data. The characteristic NMR features for iodo/bromo-substituted fluorofurans **3a**–**e**/**6a**–**e** include the ^{13}C NMR C–F signals [δ = 152.2–150.8/149.2–148.0 ppm (d, $^1J_{CF}$ = 250.1–251.7/252.0–253.4 Hz)] and C–halogen signals [δ = 57.4–56.9/89.9–89.6 ppm (d, $^2J_{CF}$ = 24.8–25.1/21.3-21.6 Hz)]. The acquired ^{19}F NMR spectra showed F–C signals (δ = 159.0–155.3/163.8–160.8 ppm for **3**/**6**) in agreement with known data.[5,15] Mass spectra for **3**/**6** exhibited intense molecular ion peaks and appropriate isotopic patterns.

The molecular structure of a representative 3,4-dihalosubstituted furan was confirmed by X-ray crystallography (Figure 1).[30] The molecule of the expected 3-fluoro-4-iodofuran **3a** (excluding H atoms) is nearly planar within 0.13 Å.

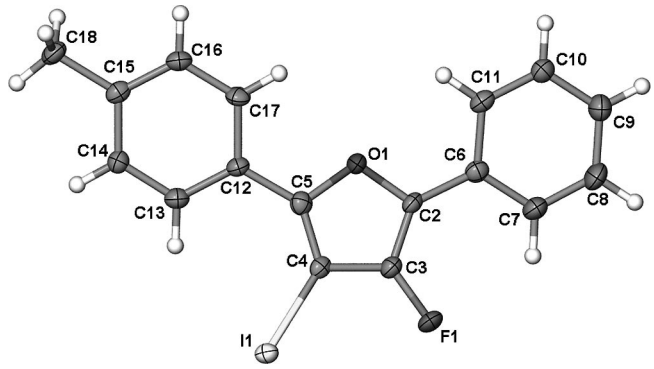
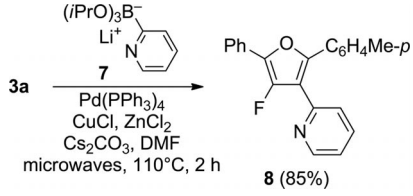


Figure 1. ORTEP view of **3a**.

The 3-fluoro-4-iodofuran **3a** was validated as a substrate for the Suzuki–Miyaura coupling reaction with a lithium N-heterocyclic trialkylborate[31] by using the conditions developed by Frontier Scientific (Scheme 3).[32] The use of lithium triisopropoxy(pyridin-2-yl)borate **7** allowed for the introduction of a pyridine moiety that would be sensitive to an acidic reaction environment. Pyridinyl-substituted 2-phenyl-3-fluoro-5-(*p*-tolyl)furan **8** was obtained in 85% yields.



Scheme 3. Coupling of iodofuran **3a**.

Conclusions

We have demonstrated that the combination of *N*-halosuccinimides with gold(I) chloride/zinc bromide is an efficient system for the iodo- and bromocyclization of fluoroalkynones **5**, which are obtained by monofluorination of the silyl enol ethers **4**. The method provides effective access to diversely 2,5-disubstituted 3-fluoro-4-halofurans. The relatively short reaction times and mild conditions (room temp.) provide an appealing protocol that includes the for-

mation of three bonds in a sequential procedure. This method avoids the loss of halogens in the synthetic pathway, facilitates the regioselective positioning of halogens within two available β-locations, and also allows for the introduction of substituents such as cyclopropyl that is not easily carried out by other methods. Iodofuran was confirmed as substrate for coupling with lithium N-heterocyclic trialkylborate. The determination of the role of the catalysts and further optimizations are the subject of further investigations in our laboratory.

Experimental Section

3-Fluoro-4-iodo-5-(4-methylphenyl)-2-phenylfuran (3a): A 50 mL round-bottom flask was charged with silyl enol ether **4a** (0.0875 g, 0.251 mmol), Selectfluor (0.098 g, 0.28 mmol), and MeCN (5 mL). The mixture was stirred at ambient temperature (22 °C) and monitored by TLC (hexanes/EtOAc, 8:2; usually for 1 h). The solvent was removed by rotary evaporation, and the residue was kept under oil-pump vacuum for 30 min. Dichloromethane (30 mL) was added, and the mixture was stirred for 10 min. The solid was filtered off (fritted funnel), and the filter cake was washed with CH_2Cl_2 (10 mL). The solvent was removed from the combined filtrates by rotary evaporation. *N*-Iodosuccinimide (0.068 g, 0.30 mmol) and anhydrous CH_2Cl_2 (5.0 mL) were added. The mixture was stirred for a few minutes to become homogeneous, and anhydrous ground $ZnBr_2$ (0.011 g, 0.049 mmol) was added followed immediately by AuCl (0.0030 g, 0.013 mmol) in anhydrous CH_2Cl_2 (3.0 mL). The mixture was stirred vigorously at ambient temperature for 10 min. The reaction was quenched by adding saturated aqueous sodium thiosulfate solution (10 mL) and stirring for few minutes. CH_2Cl_2 (30 mL) was added. The organic layer was separated, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel column chromatography (hexanes) gave **3a** (0.0720 g, 0.190 mmol, 76%) as a white solid, m.p. 115–116 °C. $C_{17}H_{12}FIO$ (378.18): calcd. C 53.99, H 3.20; found C 54.40, H 3.24. IR (KBr): $\tilde{\nu}$ = 2963, 1653, 1559, 1262, 938, 816, 668 cm^{-1}. MS (EI): *m/z* (%) = 378 (100) [M^+]. ^1H NMR ([D_6]acetone): δ = 8.05–7.97 (m, 2 H), 7.81–7.75 (m, 2 H), 7.56–7.48 (m, 2 H), 7.39–7.32 (m, 3 H), 2.40 (s, 3 H) ppm. ^{13}C ([D_6]acetone): δ = 151.8 (d, J = 250.6 Hz), 149.7 (d, J = 6.0 Hz), 140.2, 136.2 (d, J = 20.9 Hz), 130.3, 130.0, 128.9 (d, J = 5.2 Hz), 128.8, 128.1 (d, J = 1.3 Hz), 126.9, 124.5 (d, J = 5.0 Hz), 56.9 (d, J = 25.1 Hz), 21.4 ppm. ^{19}F NMR ($CDCl_3$): δ = –156.7 ppm.

Supporting Information (see footnote on the first page of this article): ^1H, ^{13}C, and ^{19}F NMR spectra for furans **3**, **6**, and **8**.

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