Room temperature syntheses of entirely diverse substituted β-fluorofurans
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IN THIS ISSUE
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Cover
See Roman Dembinski et al., pp. 2395–2408.

The cover image is related to cycloisomerization and electrophilic cyclization reactions. The methodology allows the synthesis of diversely substituted β-fluorofurans, from propargyl ketones at room temperature.

Cover art by Tomasz Sniady.


PERSPECTIVE

2351
Recent advances in the stereoselective synthesis of carbohydrate 2-C-analogs
Jian Yin and Torsten Linker*
A perspective summarizing recent syntheses of carbohydrate 2-C-analogs 1 by ring-opening of cyclopropanated sugars 3 and radical additions to glycals 2 is given.

COMMUNICATIONS

2363
Intramolecular iron(II)-catalyzed aminobromination of allyl N-tosylxycarbamates
Takuma Kamon, Daisuke Shigeoka, Tetsuaki Tanaka and Takehiko Yoshimitsu*

Allyl N-tosylxycarbamates are found to be catalytically transformed into β-brominated oxazolidinones with FeBr$_2$/n-Bu$_4$NBr in t-BuOH.
Room temperature syntheses of entirely diverse substituted β-fluorofurans†

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Synthesis of highly substituted 3-fluorofurans is reported. The sequence began with preparation of tert-butyldimethylsilyl alk-1-en-3-yn-1-yl ethers from 1,4-disubstituted alk-3-yn-1-ones. Subsequent fluorination of alkenynyl silyl ethers with Selectfluor gave 2-fluoroalk-3-yn-1-ones in almost quantitative yield. Subsequent 5-endo-dig cyclizations using chlorotriphenylphosphine gold(i)/silver trifluoromethanesulfonate (5/5 mol%), N-bromo- or N-iodosuccinimide and gold(i) chloride/zinc bromide (5/20 mol%), all at room temperature, provided a facile method for the generation of substituted 3-fluoro-, 3-bromo-4-fluoro-, and 3-fluoro-4-iodofurans in good yields. Also, 2,2-difluoroalk-3-yn-1-ones were prepared by fluorination of alk-3-yn-1-ones under organocatalytic conditions. The structures of (Z)-tert-butyldimethylsilyl but-1-en-3-yn-1-yl ether, 3-bromo-4-fluorofuran, and 3-fluoro-4-(phenylethynyl) furan were confirmed by X-ray crystallography.

Introduction

Active pharmaceutical ingredients incorporating the fluorine atom have found wide applications in the field of medicinal chemistry.1,2 Currently, fluorine-containing compounds are leading in the list of best-selling drugs.3 In fact, fluorofuran or perfluoralkylfuranyl fragments have already been embedded within structures possessing interesting pharmacological properties.4,5 Since the furan ring constitutes a submotif of medicinal interest,6 corresponding fluorinated molecules are highly sought after building blocks. Thus, upon considering the pharmacological potential, as well as the limitations of available synthetic methods for 3-fluorofurans, we decided to pursue the development of their synthesis.

Halofurans are important derivatives, extensively utilized for the preparation of acyclic, carbocyclic, and heterocyclic compounds. In addition, halofurans provide an opportunity for further functionalization. In particular, iodo-, bromo-, and also recently chlorofurans have been useful substrates for a variety of bond-forming reactions.7–11 In general, approaches to the synthesis of β-halofurans can be divided into substitution reactions on the furan core and the construction of a furan ring starting from acyclic precursors.12,13 The later centers on cycloisomerization or cyclocondensation reactions and includes halogenation/cyclizations, and cyclizations of precursors that contain already introduced halogens. Electrophilic cyclization reactions are particularly attractive since they provide versatile access to different halofurans by treatment of the same starting material with different halogens.14,15 Usually the electrophile acts as both the cyclization initiator and a halogen donor, thus fostering material economy. However, fluorine, due to its limited electrophilic character, is not effective in electrophilic cyclizations.16 So far, preparative access to 3-fluorofurans includes only a few specific methods; the syntheses usually encompass aggressive conditions or poor yields.12

Only scarce reports provide a preparative route to β,β′-difluorohalofurans, which offer an opportunity for further functionalization of fluorofurans. Theiodicyclization of gem-difluoro homoaryl alcohols (2,2-difluoroalk-3-yn-1-ols) can be induced by iodine monochloride in the presence of a base and microwave irradiation.7 Subsequent silica gel aromatization of 3,3-difluoro-4-iodo-2,3-dihydrofurans leads to the 3-fluoro-4-iodofurans. Only one example of 3-bromo-4-fluorofuran, prepared by a sequential lithiation/bromination reaction of 3-fluoro-2,5-diphenylfuran, has been reported with undisclosed preparative yield.17

In order to access a family of β-fluorofurans (1), we elected to introduce fluorine into an acyclic skeleton and to use 2-fluoroalk-3-yn-1-ones (2) as a versatile cyclization starting material (Scheme 1).18,19 Fluoroalkynone 2 contains one less fluorine...