

A New and Concise Synthesis of 3-Fluoro-2,5-disubstituted Furans

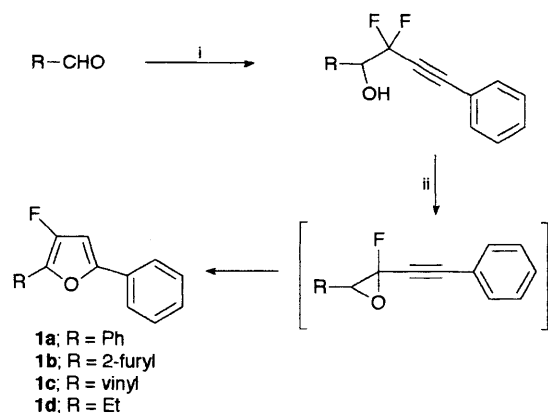
Hing L. Sham* and David A. Betebenner

Abbott Laboratories, Pharmaceutical Discovery Division, Department 47D, Abbott Park, Illinois 60064-3500 USA

A highly efficient synthesis of a series of 3-fluoro-2,5-disubstituted furans by a two-step sequence is described.

Furans¹ are perhaps one of the most prominent classes of heteroaromatic compounds with widespread occurrence in nature.² The furan nucleus is also incorporated in a wide variety of commercially important pharmaceuticals and flavour/fragrance compounds.³ Although numerous synthetic routes to furans are reported,^{1,4} the syntheses of

fluorine-substituted furans are very few and are not regio-specific. From a biological point of view, fluoro-substitution often confers unique properties to a molecule in terms of increased lipophilicity, which in turn changes *in vivo* absorption and transport rates. One of the earlier reports⁵ on the synthesis of polyfluorinated furans by the fluorination of



Scheme 1 Reagents: i, bromodifluoromethylphenylacetylene, Zn; ii, potassium *tert*-butoxide-*tert*-butyl alcohol

tetrahydrofuran, followed by dehydrofluorination with molten potassium hydroxide provided a random mixture of polyfluorofurans in relatively low yields. We report here a new and concise synthesis of 3-fluoro-2,5-disubstituted furans.

Our regiocontrolled synthesis of 3-fluorofurans is based on a two-step sequence: (i) Reformatsky reaction of bromodifluoromethylphenylacetylene⁶ with an aldehyde; (ii) base-promoted cyclisation of the resultant difluoro-alcohol to provide the corresponding furan. The sequence is illustrated using benzaldehyde as example. Similar results (see Table 1) were obtained with heteroaromatic aldehyde (2-furaldehyde), α,β -unsaturated aldehyde (acrolein) or aliphatic aldehyde (propionaldehyde). Slow addition of bromodifluoromethylphenylacetylene (1.5 equiv.) to a solution of benzaldehyde in tetrahydrofuran (THF) with zinc dust and 5 mol% of HgCl_2 under sonicating conditions at room temperature provided the corresponding difluoro-alcohol in 74% yield (see Scheme 1). Treatment of the α,α -difluoro-alcohol with potassium *tert*-butoxide in *tert*-butyl alcohol provided 3-fluoro-2,5-diphenylfuran in 98% yield. The cyclisation may go through an acetylenic epoxide intermediate. Analogous isomerisation by potassium *tert*-butoxide of an allenic epoxide into a furan has been reported.⁷ By this methodology, the 2-substituent can be readily varied simply by choosing the appropriate aldehyde as the starting material.

Table 1 Yields^a and ¹H and ¹⁹F NMR data^b

I	Yield (%)	H ₄ (δ)	F ₃ (δ)
a R = Ph	98	6.68	161.9
b R = 2-furyl	97	6.66	163.2
c R = vinyl	90	6.56	164.7
d R = Et	91	6.50	172.7

^a Yields are for the cyclisation step. ^b ¹H NMR data are in ppm downfield from tetramethylsilane as internal standard; ¹⁹F NMR data are in ppm upfield from CFCl_3 as internal standard in CDCl_3 .

In conclusion, a highly efficient and regiocontrolled synthesis of 3-fluoro-2,5-disubstituted furans[†] is described. The application of this methodology to the synthesis of biologically active fluoro-furans will be reported in the future.

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[†] All new compounds have satisfactory spectral and elemental analysis.