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

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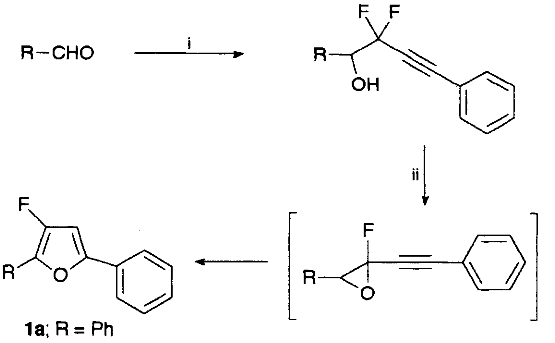
A highly efficient synthesis of a series of 3-fluoro-2,5-disubstituted furans by a two-step sequence is described.

Furans[1] 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 regiospecific. 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 reports[5] on the synthesis of polyfluorinated furans by the fluorination of



**1a**; R = Ph
**1b**; R = 2-furyl
**1c**; R = vinyl
**1d**; R = Et

**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 bromodifluoromethylphenylacetylene[6] 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 $^{19}F$ NMR data[b]

| 1 | | 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; $^{19}F$ 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.

We thank Mr Momir Cirovic of the Analytical Department, Abbott Laboratories for obtaining the $^{19}F$ NMR spectra.

*Received, 24th May 1991; Com. 1/02461B*

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† All new compounds have satisfactory spectral and elemental analysis.