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Synthesis of cicerfuran, an antifungal benzofuran, and some related analogues

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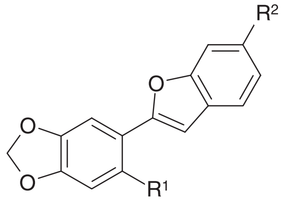
Abstract—Routes were investigated for the synthesis of cicerfuran, a hydroxylated benzofuran from wild chickpea implicated in resistance to Fusarium wilt, and some of its analogues. A novel method is described for the synthesis of oxygenated benzofurans by epoxidation and cyclisation of 2′-hydroxystilbenes. The stilbene intermediates required could be synthesised by palladium-catalysed coupling of styrenes with mono-oxygenated aryl halides but not with di-oxygenated aryl halides. Stilbenes corresponding to the latter were synthesised by Wittig reactions.

1. Introduction

Benzofurans and their analogues constitute a major group of naturally-occurring compounds that are of particular interest because of their biological activity and role in plant defence systems.[1] The hydroxylated benzofuran cicerfuran (**1a**, Fig. 1) was first obtained from the roots of a wild species of chickpea, *Cicer bijugum*, and reported to be a major factor in the defence system against Fusarium wilt.[2]



1a R^1=OMe, R^2=OH
1b R^1=H, R^2=H
1c R^1=OMe, R^2=H
1d R^1=Me, R^2=H
1e R^1=H, R^2=OH
1f R^1=Me, R^2=OH

Figure 1. Structures of cicerfuran (**1a**) and analogues (**1b–f**).

Several methodologies are available for the synthesis of simple benzofurans[3] but less attention has been given to the synthesis of hydroxylated benzofurans. Methodologies reported to date for the synthesis of natural hydroxylated benzofurans involve formation of a C–C bond between benzofuran and a substituted aryl halide,[4] arylation of a benzofuranone,[5] cyclisation of an arylbenzylketone,[6] coupling of cuprous acetylides with aryl halides,[7] Sonogashira coupling of terminal acetylenes with aryl halides,[8] coupling of a diphenylketone with the lithium salt of trimethylsilyldiazomethane[9] and use of an intramolecular Wittig reaction.[10]

Recently, the first synthesis of cicerfuran (**1a**) was reported by Sonogashira coupling of 2-methoxy-4,5-methylenedioxyphenylacetylene with dioxygenated aryl halides.[11] Our study employs an alternative strategy for the production of both cicerfuran and related analogues and was developed independently of the work of Novak and colleagues.[11] The essential features (Scheme 1) are palladium-catalysed coupling of a styrene and a 2-hydroxyaryl halide to generate a stilbene, followed by epoxidation, cyclisation and dehydration.

Two analogues (**1c**, **1d**) of cicerfuran (**1a**) were synthesised successfully by this method, but the palladium coupling step did not proceed with the dioxygenated aryl halides that are required for synthesis of cicerfuran itself (Scheme 1, R_2 = OH). Palladium-catalysed coupling of the more reactive aryl acetylenes[12–14] with 2-iodophenol proceeded well to give two analogues (**1b**, **1c**) of cicerfuran directly. Use of this approach, essentially as described by Novak

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Keywords: Cicerfuran; Arylbenzofuran; Palladium-catalysed coupling; Wittig reaction.

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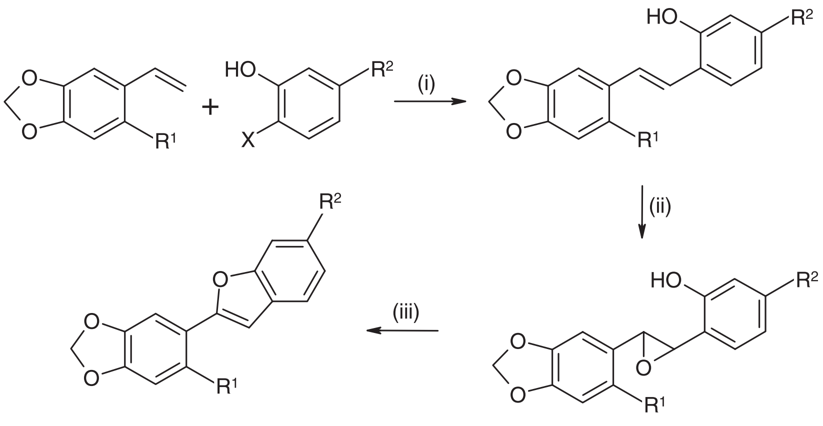


Scheme 1. Reagents and conditions: (i) palladium catalyst; (ii) epoxidation; (iii) mild acid.

et al.[11] gave cicerfuran (**1a**) only in low yields. Returning to the original synthetic plan, the stilbene required was synthesised by a Wittig reaction between 2-methoxy-4,5-methylenedioxybenzyltriphenylphosphonium bromide and 2,4-di-*tert*-butyldimethylsiloxy-benzaldehyde. Epoxidation and cyclisation gave an alternative route to cicerfuran (**1a**) in quantities sufficient for further biological assays. In addition, the synthetic and natural cicerfuran were compared directly and shown to have identical spectroscopic and chromatographic properties, confirming the proposed structure for the natural compound. Two further analogues (**1e**, **1f**) of cicerfuran were prepared by this route but were not characterised fully due to decomposition during the purification.

2. Results and discussion

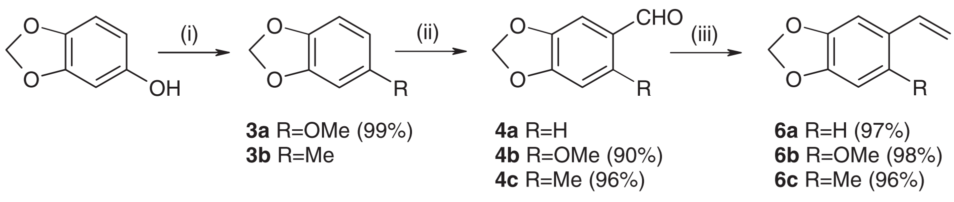
2.1. Synthesis of benzofurans via palladium-catalysed coupling of styrenes and aryl halides

2.1.1. Synthesis of styrenes. Styrene precursors for use in palladium-catalysed coupling (Scheme 1) were styrene itself (**5**) and methylenedioxystyrenes (**6a–c**) prepared from the corresponding benzaldehydes (**4a–c**) by a Wittig reaction with methyltriphenylphosphonium bromide and *n*-butyllithium (Scheme 2). 3,4-Methylenedioxystyrene (**6a**) was obtained in 97% yield from piperonal (3,4-methylenedioxybenzaldehyde) (**4a**).

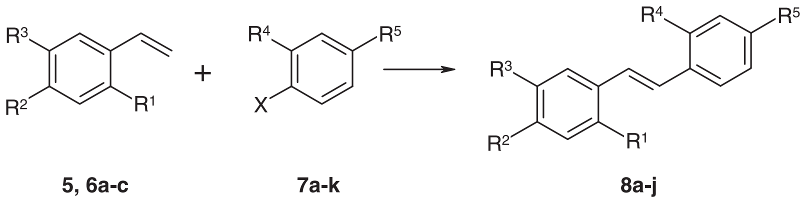
Sesamol (3,4-methylenedioxyphenol) (**2**) was *O*-methylated using sodium hydroxide and dimethylsulphate to give anisole **3a** in 99% yield. Formylation[15] of **3a** gave benzaldehyde **4b** in 90% yield as shown in Scheme 2. The benzaldehyde **4b** was then converted to the desired styrene **6b** by a Wittig reaction in 98% yield.

2-Methyl-4,5-methylenedioxybenzaldehyde (**4c**) was similarly obtained in 96% yield by formylation of commercially-available 3,4-methylenedioxytoluene (**3b**) and 2-methyl-4,5-methylenedioxyphenyl-ethene (**6c**) was obtained in 96% yield via a Wittig reaction of **4c** under the same reaction conditions (Scheme 2).

2.1.2. Palladium-catalysed coupling of styrenes with aryl halides. Palladium-catalysed reactions are among the most frequently used methods for carbon–carbon bond formation and have been applied to synthesis of both natural and non-natural compounds.[16–19] Experiments were carried out to optimise the reaction conditions for the palladium-catalysed coupling of styrenes **5** and **6a** with simple aryl halides and then with multioxygenated aryl halides (Scheme 3, Table 1).



Scheme 2. Reagents and conditions: (i) NaOH, $(CH_3)_2SO_4$; (ii) α,α-dichloromethylmethyl ether, $TiCl_4$; (iii) *n*-BuLi, THF, methyltriphenylphosphonium bromide.



Scheme 3. Palladium-catalysed coupling of styrenes with aryl halides.