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

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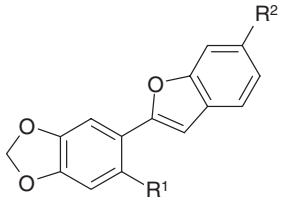
Abstract—Routes were investigated for the synthesis of cicerfuran, a hydroxylated benzofuran from wild chickpea implicated in resistance to Fusarium wilt, and some of its analogues. A novel method is described for the synthesis of oxygenated benzofurans by epoxidation and cyclisation of 2′-hydroxystilbenes. 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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